Cognitive and behavioral outcome after solid organ transplantation in childhood

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ABSTRACT

Organ transplantation (Tx) is a life-saving procedure for patients with end-stage organ failure. Survival rates have improved in recent decades, but the prevalence of neurological and psychiatric morbidities remain high. Pediatric heart, kidney, and liver Tx recipients generally perform in the low-average to average range in global intelligence. Comprehensive evaluations of other neuropsychological functions are rare. More studies of behavioral outcome – that is, health-related quality of life (HRQOL) and psychosocial adjustment (PSA) – have been published with outcomes generally lower than those reported in the general population and similar to those of children with other chronic diseases. Few studies have compared adjustment between children who have undergone different types of organ Tx.

This is the first study to comprehensively assess cognitive and behavioral outcomes in a national sample of Finnish children who have undergone heart, kidney, or liver Tx. The thesis consists of four original studies that present data on 87 children who received transplants between 1993 and 2008. The first aim of this thesis was to assess both global intelligence and specific neuropsychological outcome in pediatric heart, kidney, and liver Tx recipients in the domains of attention, language, sensorimotor and visuospatial functions, memory and learning, and social processing. The second aim of this thesis was to compare HRQOL and PSA between the Tx groups.

Within the cognitive outcome variables, a generalized effect on intelligence was observed, on a group level, in children who underwent heart or kidney Tx, particularly in children with neurological or neuroradiological abnormality. Liver Tx children had age-appropriate intelligence. All Tx groups tended to have more problems in nonverbal than in verbal intelligence. In neuropsychological functions, specific visuomotor and visuoconstructive impairment emerged in all Tx groups. In children without neurological comorbidity, few problems emerged in attention, language, or memory and learning. Parents reported difficulties in the same functions, as demonstrated through cognitive assessment, except for an increase in problems in memory and learning in the parental evaluations. Of the risk factors, early onset and longer disease duration prior to Tx were associated with poorer cognitive outcome, particularly in

nonverbal functions. Also, poorer graft function at the time of assessment was associated with lower verbal/auditory functions and memory in kidney Tx children.

Within the behavioral outcome variables, no significant differences were observed in HRQOL or PSA between the Tx groups. Parents and teachers reported an increase in internalizing and in the total number of psychiatric symptoms, but these were attributable mainly to a significant increase in somatic complaints. Younger Tx children reported lower HRQOL than did adolescent patients. However, both age groups found that their health made it more difficult to be with friends, for example, and attend school or hobbies. Of the risk factors, shorter follow-up time after Tx was associated with poorer behavioral outcome. Neurological comorbidity was associated with both self-reported HRQOL and proxy-reported PSA, yet family structure (child not living with both biological parents) and poorer parental HRQOL were also negatively associated with the child's PSA.

The outcomes of the majority of school-aged children who have undergone a solid organ Tx are reassuring. However, a significant minority exhibit considerable global cognitive delay. Additionally, the cognitive profile suggests that Tx children may be susceptible to negative effects in the posterior cortex with associated visuospatial difficulties. Thus, follow-up evaluations of children who have undergone Tx need to include assessment of both intelligence and of other neuropsychological functions, particularly in the domains of visuomotor, visuoconstructive, and visuospatial functions. Further, Tx children and their families should be offered psychosocial support. During cognitive and socioemotional development, new issues may arise; consequently, counseling as a routine part of treatment throughout childhood and adolescence is essential.

TIIVISTELMÄ

Moderni lääketiede pystyy elinsiirtoleikkausten avulla pelastamaan kasvavan määrän lapsia, joiden elämä on ollut uhattuna. Eloonjäämisluvut ovat parantuneet viime vuosikymmenten aikana, mutta neurologisten ja psykiatristen ongelmien esiintyvyys on pysynyt korkeana. Sydän-, munuais- tai maksansiirron saaneiden lasten suoriutuminen älykkyystesteissä sijoittuu ryhmätasolla alhaisen keskitason ja keskitason välille. Kattavia tutkimuksia muista neuropsykologisista toiminnoista on vähän. Behavioraalisia muuttujia eli terveyteen liittyvää elämänlaatua ja psykososiaalista sopeutumista on tutkittu laajemmin. Tulokset ovat yleisesti huonompia verrattuna väestön keskiarvoon, mutta samanlaisia kuin muilla pitkäaikaissairailla lapsilla. Harvat tutkimukset ovat verranneet sopeutumista eri siirtoryhmien välillä.

Tämä on ensimmäinen kattava tutkimus kognitiivisista ja behavioraalisista muuttujista kansallisessa otoksessa sydän-, munuais- tai maksansiirron saaneista suomalaislapsista. Väitöskirja koostuu neljästä alkuperäisestä tutkimuksesta, jotka esittelevät vuosina 1993-2008 elinsiirron saaneiden 87 lapsen tuloksia. Väitöskirjan ensimmäinen päätarkoitus oli tutkia sydän-, munuais- tai maksansiirron saaneiden lasten yleistä älykkyyttä sekä tarkemmin neuropsykologisia toimintoja seuraavilla alueilla: tarkkaavuus, kielelliset toiminnot, sensomotoriset ja visuospatiaaliset toiminnot, muisti ja oppiminen sekä sosiaalinen havaitseminen. Väitöskirjan toinen päätarkoitus oli verrata terveyteen liittyvää elämänlaatua ja psykososiaalista sopeutumista siirtoryhmien välillä.

Kognitiivisissa muuttujissa laaja-alainen vaikutus älylliseen suorituskykyyn oli huomattavissa ryhmätasolla sydän- ja munuaissiirron saaneilla lapsilla. Tämä koski erityisesti lapsia, joilla oli todettu neurologisia tai neuroradiologisia poikkeavuuksia. Maksansiirron saaneilla lapsilla älyllinen suorituskyky oli ikätasoista. Kaikissa siirtoryhmissä havaittiin enemmän vaikeuksia ei-kielellisessä kuin kielellisessä älykkyydessä. Neuropsykologisissa toiminnoissa vaikeuksia ilmeni visuomotorisissa ja visuokonstruktiivisissa toiminnoissa kaikissa siirtoryhmissä. Lapsilla, joilla ei ollut neurologisia poikkeavuuksia ei yleisesti ollut ongelmia tarkkaavuudessa, kielellisissä toiminnoissa tai muistissa ja oppimisessa. Vanhemmat raportoivat ongelmia samoilla

toiminnan alueilla kuin mitä ilmeni kognitiivisessa tutkimuksessakin. Lisäksi vanhemmat raportoivat enemmän ongelmia muistin ja oppimisen alueilla. Riskitekijöistä varhainen sairastuminen ja pidempi sairausaika ennen siirtoa olivat yhteydessä huonompiin kognitiivisiin tuloksiin, erityisesti ei-kielellisissä toiminnoissa. Lisäksi heikompi siirteen toiminta tutkimuksen ajankohtana oli yhteydessä huonompiin kielellisiin/auditiivisiin toimintoihin ja muistiin munuaissiirron saaneilla lapsilla.

Behavioraalisissa muuttujissa terveyteen liittyvä elämänlaatu ja psykososiaalinen sopeutuminen eivät eronneet siirtoryhmien välillä. Vanhemmat ja opettajat raportoivat enemmän sisäänpäin suuntautuneita ongelmia ja psykiatristen oireiden kokonaisesiintyvyyttä, mikä johtui pääasiassa somaattisten oireiden kohonneesta määrästä. Nuoremmat potilaat arvioivat terveyteen liittyvän elämänlaatunsa huonommaksi kuin murrosikäiset potilaat. Kummatkin ikäryhmät raportoivat terveytensä vaikuttavan mm. ystävien kanssa vietettyyn aikaan ja koulunkäyntiin tai harrastuksiin. Riskitekijöistä pidempi seuranta-aika siirrosta oli tärkeä lieventävä tekijä behavioraalisissa muuttujissa. Neurologinen komorbiditeetti oli yhteydessä sekä lasten omaan arvioon elämänlaadustaan että vanhempien ja opettajien arvioon lasten sopeutumisvaikeuksista. Myös perherakenne (lapsi ei asunut kummankin biologisen vanhempansa kanssa) ja vanhempien oma heikentynyt terveyteen liittyvä elämänlaatu olivat yhteydessä lasten huonompaan sopeutumiseen.

Enemmistöllä kouluikäisistä elinsiirtolapsista toimintataso on hyvä. Merkittävällä vähemmistöllä on kuitenkin huomattavan laaja-alaisia kognitiivisen kehityksen ongelmia. Tämän lisäksi siirron saaneiden lasten kognitiivinen profiili viittaa vaurioihin aivokuoren taemmissa osissa ja näihin liittyviin visuospatiaalisiin ongelmiin. Siirtolasten seurannassa tulisi näin ollen yleisen älykkyyden lisäksi tutkia muita neuropsykologisia toimintoja huomioiden erityisesti visuomotoriset, visuokonstruktiiviset ja avaruudellisen hahmottamisen ongelmat. Siirtolapsille ja heidän perheilleen tulisi lisäksi tarjota psykososiaalista tukea. Tavanomaisen kognitiivisen ja sosioemotionaalisen kehityksen myötä saattaa ilmetä uudenlaisia kysymyksiä ja psyykkisen tuen tulisikin olla olennainen osa lasten saamaa hoitoa läpi lapsuuden ja nuoruuden.

SAMMANFATTNING

Organtransplantation är en livräddande behandling för patienter med organsvikt. Under de senaste årtionden har chanserna för överlevnad kontinuerligt förbättrats. Trots detta förblir förekomsten av neurologisk och psykiatrisk komorbiditet hög. Barn som genomgått en hjärt-, njur- eller levertransplantation uppvisar generellt en intelligens som ligger mellan låg normalzon och normalzon. Det finns få omfattande utredningar av andra neuropsykologiska funktioner. Ett flertal studier har behandlat beteendemässiga variabler som hälsorelaterad livskvalitet och psykosocial anpassning. Resultaten är generellt under populationsmedelvärden och likartade som för barn med andra kroniska sjukdomar. Enbart ett fåtal studier har jämfört anpassning mellan olika pediatriska transplantationsgrupper.

Detta är den första omfattande utredningen av kognitiva och behaviorala variabler i ett nationellt urval av finska barn som genomgått en hjärt-, njur- eller levertransplantation. Avhandling består av fyra delstudier som presenterar data på 87 barn som genomgått organtransplantation mellan 1993 och 2008. Avhandlingens första syfte var att utvärdera både intelligens och specifika neuropsykologiska funktioner hos barn som genomgått en hjärt-, njur- eller levertransplantation inom följande områden: uppmärksamhet, språk, sensomotoriska och visuospatiala funktioner, minne och inlärning samt social perception. Avhandlingens andra syfte var att jämföra hälsorelaterad livskvalitet och psykosocial anpassning mellan transplantations-grupperna.

Hos barn som genomgått en hjärt- eller njurtransplantation observerades på gruppnivå en påverkan på intelligens, speciellt hos barn med neurologisk eller neuroradiologisk avvikelse. Barn som genomgått en levertransplantation hade däremot åldersenlig intelligens. Alla grupper tenderade ha mera problem inom nonverbal än verbal intelligens. Barn som genomgått en organtransplantation hade därtill specifika visuomotoriska och visuokonstruktiva svårigheter. Hos gruppen barn utan neurologisk avvikelse framkom få problem med uppmärksamhet, språk eller minne och inlärning. Föräldrarnas rapportering av funktionsnedsättningar överensstämde med resultaten från den kognitiva utredningen. Föräldrarna rapporterade därtill problem med minne och

inlärning. Tidig sjukdomsdebut och en längre sjukdomstid före transplantationen var associerade med sämre kognitiva resultat, speciellt i nonverbala funktioner. Det visade sig också att en sämre organfunktion vid tidpunkten för studien var associerad med sämre verbal/auditiv funktion och minne hos njurtransplanterade barn.

Mellan transplantationsgrupperna observerades inga skillnader i hälsorelaterad livskvalitet eller psykosocial anpassning. Föräldrar och lärare rapporterade förhöjda inåtvända (internaliserade) och totala antal psykiska problem, men dessa berodde främst på en signifikant ökning i antalet somatiska symptom. Yngre barn rapporterade lägre hälsorelaterad livskvalitet än tonåringar. Båda åldersgrupperna upplevde att deras hälsotillstånd försvårade bl.a. förmågan att umgås med vänner och att delta i skolgång eller hobbyn. Kortare uppföljningstid efter transplantationen var associerad med mera beteendemässiga problem. Neurologisk komorbiditet påverkade både barnens egen utvärdering av sin livskvalitet samt föräldrarnas och lärarnas rapportering av psykosociala anpassningssvårigheter. Även familjestruktur (barnet bodde inte med sina båda biologiska föräldrar) och sämre hälsorelaterad livskvalitet hos föräldrarna var associerade med sämre anpassning hos barnet.

Majoriteten av barn i skolåldern som genomgått en organtransplantation har en bra funktionsnivå. En betydande minoritet uppvisar ändå omfattande problem i den kognitiva utvecklingen. Dessutom tyder den kognitiva profilen på en benägenhet för negativa effekter i hjärnbarkens posteriora delar, vilket är förknippat med visuospatiala svårigheter. I uppföljningen är det därför nödvändigt att utvärdera både allmän intelligens såväl som specifika neuropsykologiska funktioner, med särskild tonvikt på de visuomotoriska, visuokonstruktiva och visuospatiala funktionerna. Familjer med barn som genomgått en organtransplantation borde även erbjudas psykosocialt stöd. Detta stöd borde erbjudas som en väsentlig del av vården under hela uppväxten eftersom nya frågor kan uppstå under barnets kognitiva och socioemotionella utveckling.

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> "…a world that is strange and does not fit our usual expectation of an experience… This is the world of transplantation. This strange world involves the gift of donation, the possibility of rejection, and even untimely death. The gift comes with a price tag. It is a complicated extension of the children's will to live and their families' refusal to give up hope. Families are willing to travel into unknown territory with an uncertain future because the life of their child is precious."
>
> Barbara V. Wise, In their Own Words: The Lived Experience of Pediatric Liver Transplantation, Qualitative Health Research, 2002; 12; 79-80.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, referred to in the text by Roman numerals I to IV.

I Haavisto, A., Korkman, M., Jalanko, H., Holmberg, C., & Qvist, E. (2010). Neurocognitive function of pediatric heart transplant recipients. *Journal of Heart and Lung Transplantation, 29*, 764-770.

II Haavisto, A., Korkman, M., Holmberg, C., Jalanko, H., & Qvist, E. (2012). Neuropsychological profile of children with kidney transplants. *Nephrology, Dialysis and Transplantation, 27,* 2594-2601.

III Haavisto, A., Korkman, M., Törmänen, J., Holmberg, C., Jalanko, H., & Qvist, E. (2011). Visuospatial impairment in children and adolescents after liver transplantation. *Pediatric Transplantation, 15,* 184-192.

IV Haavisto A., Korkman M., Sintonen H., Holmberg C., Jalanko H., Lipsanen J., & Qvist E. (2013). Risk factors for impaired quality of life and psychosocial adjustment after pediatric heart, kidney, and liver transplantation. *Pediatric Transplantation, 17,* 256-265.

 In addition, some unpublished data are presented.

ABBREVIATIONS

ANOVA	analysis of variance
ASEBA	Achenbach System of Empirically Based Assessment
CHD	congenital heart disease
CNF	congenital nephrosis of the Finnish type
FSIQ	Full-Scale Intelligence Quotient
HRQOL	health-related quality of life
NEPSY-II	NEPSY-II: A Developmental Neuropsychological Assessment
PIQ	Performance Intelligence Quotient
PSA	psychosocial adjustment
SD	standard deviation
Tx	transplantation
VIQ	Verbal Intelligence Quotient
WISC-III	Wechsler Intelligence Scale for Children, 3rd edition

1 INTRODUCTION

The first attempts at pediatric organ transplantation (Tx) took place in the 1950s and 1960s. Since then, medical advances have dramatically increased survival rates and improved long-term outcome. At the turn of the millennium, the first survivors of pediatric solid organ Tx successfully entered adulthood (Groothoff, 2005). Since survival rates have improved, the research focus is switching from merely medical aspects to cognitive and behavioral outcome. However, few comprehensive neuropsychological evaluations in this patient population have been published. Health-related quality of life (HRQOL) and psychosocial adjustment (PSA) have been studied more extensively, but few studies have compared adjustment in children who have undergone different types of organ Tx.

The most commonly transplanted organs are the kidney, liver, and heart. In Finland, the first pediatric kidney, liver, and heart Tx took place in 1986, 1987, and 1991, respectively. Currently, patient five-year survival rates are 97%, 77%, and 83%, for kidney, liver and heart Tx (Transplantation Registry Report: Children's Hospital, 2006). These rates are comparable to those from centers around the world (Kirk et al., 2011; Smith, Stablein, Munoz, Hebert, & McDonald, 2007; Soltys et al., 2007).

Children who have undergone organ Tx are a heterogeneous patient group. The majority of these children have a congenital disease which may have compromised their early development, even prenatally. A minority experiences a healthy infancy with sudden disease onset in later childhood. Studies on the cognitive and behavioral outcome in the first Tx patients treated – particularly kidney Tx children – have been undertaken at the Childrens's Hospital in Helsinki (Apajasalo, Rautonen, Sintonen, & Holmberg, 1997; Qvist et al., 2002; Qvist et al., 2004; Valanne, Qvist, Jalanko, Holmberg, & Pihko, 2004). This thesis focuses on the cognitive and behavioral outcome in a recent cohort of Finnish heart, kidney, and liver Tx patients.

1.1 End-stage organ failure and transplantation in childhood

End-stage organ failure places a child at risk for malnutrition, growth failure, infections, and cardiovascular insult, all of which are a risk for development. A longer waiting time for Tx prolongs the time spent in organ failure, with its deleterious effects. The patients undergo painful medical and surgical procedures affecting both their emotional and physical development. In addition, all patients experience hospitalizations which interrupt family life, day care or school, and normal social interaction. Moreover, other medical risk factors, such as prematurity and the presence of genetic syndromes, are overrepresented in this patient population, which may affect neurological outcome.

Other risks are also associated with the Tx operation itself, especially in heart and liver Tx. In liver Tx, the vena cava is cross-clamped for 30-60 minutes, leading to decreased cardiac output and altered hemodynamics (Fine, Webber, Harmon, Kelly, & Olthoff, 2007; Harjula & Höckerstedt, 1995). Heart Tx involves cardiopulmonary bypass and circulatory arrest. As discussed by Sarajuuri and colleagues, both methods are associated with cerebral autoregulation disturbance, microembolic injury, and a systemic inflammatory response (Sarajuuri et al., 2007), and, thus, with possible neurodevelopmental consequences (Bellinger et al., 2003; Sarajuuri et al., 2007).

After organ Tx, the receiver's immune system responds to the donor antigens. Lifelong immunosuppressive medication is necessary to avoid graft rejection. Patients receive higher doses in the early post-operative period, followed by low doses of different immunosuppressive drugs in combination to obtain the best therapeutic outcome with the fewest side-effects (Fine et al., 2007; Webber, McCurry, & Zeevi, 2006). Side-effects to medication include mild medical symptoms such as susceptibility to infections, headache, and hypertension, as well as severe symptoms such as kidney dysfunction and malignancies (Schonder, Mazariegos , & Weber, 2010; Uutela, Qvist, Holmberg, Pihko, & Jalanko, 2009). Cosmetic side-effects, such as hirsutism, gingival hyperplasia, acne, and skin infections, are also common (Schonder et al., 2010). Some side-effects, such as tremor, are commonly considered reversible; more symptoms

appear with higher doses of medication administered early post-operatively (Harjula & Höckerstedt, 1995).

Neurological complications are also common, particularly during the first months post-Tx, and have been reported in up to 35% of pediatric liver Tx recipients (Erol, Alehan, Ozcay, Canan, & Haberal, 2007). The most common neurological complications are seizures, encephalopathy, posterior reversible encephalopathy syndrome, central nervous system infection, and cerebrovascular accidents (Fernandez et al., 2010; LaRosa, Jorge Baluarte, & Meyers, 2011). Neurological complications are often associated with the introduction of immunosuppressive medication and may be reversed by reducing medication (Erol et al., 2007). The etiology of neurotoxicity is poorly understood and may occur even though the dosage falls in the therapeutic range (Bartynski et al., 2001).

1.1.1 Heart failure

The most common indications for heart Tx in childhood are congenital heart disease (CHD) and cardiomyopathy (Kirk et al., 2011). CHD develops early in fetal development and results in structural defects of the heart or the vessels carrying blood to and from the heart. These diagnoses include hypoplastic left heart syndrome, Tetralogy of Fallot, transposition of the great arteries, and pulmonary atresia. Newborns with CHD are at risk for hypoxemia (low blood oxygen), hypotension (low blood pressure), and diminished cerebral blood flow (Licht et al., 2004). Hypoxemia has been associated with cognitive and behavioral effects (Bass et al., 2004) and low cerebral blood flow with an increased incidence of periventricular leukomalacia in children with CHD (Licht et al., 2004). Most cases of severe heart disease are diagnosed within the first few months of life. These children regularly undergo one or more corrective heart surgeries, which expose them to cardiopulmonary bypass, and possibly to circulatory arrest. In some cases, a mechanical ventricular assist device is implanted to bridge the time to Tx (Jahnukainen et al., 2013).

Cardiomyopathy usually presents later and with acute onset. It affects the heart muscle, leading to heart failure. Its etiology is often unknown, but more and more

genetic diseases are detected (Bhati, Sheridan, Mill, & Selzman, 2005). Some of these may be part of a syndrome that also includes neurological symptoms. However, cardiomyopathy has generally not been associated with adverse brain outcomes. In our patient sample, children who had undergone heart Tx were on average slightly older at the time of Tx compared to the other Tx groups.

1.1.2 Kidney failure

The most common indications for kidney Tx in children worldwide are congenital malformations leading to obstruction of urinary flow (urethral valve), different stages of kidney malformations (dysplasia), and inflammations of small kidney vessels (glomerulonephritis). In Finland, however, the most common disease leading to pediatric Tx is congenital nephrosis of the Finnish type (CNF). The basic characteristic of CNF is the fulminant loss of protein through the kidneys, which occurs already in utero (Jalanko, 2009). At the Childrens's Hospital in Helsinki, children with CNF undergo bilateral nephrectomy when they attain the critical weight of 7 kg, after which they receive night time peritoneal dialysis in the home. Kidney Tx is performed when the child weighs over 9 kg, usually between the ages of one and two. In the youngest patients, the procedure is complicated by the difference in size between the adult-size kidney and the small patient, which may increase the risk of thrombosis and ureteral complications (Jalanko, 2009).

In end-stage kidney disease, or uremia, waste products that are normally filtered by the kidneys to form urine remain in the blood. This may lead to uremic encephalopathy, characterized by an altered mental status and, if left untreated, coma and death (Stewart, Kennard, Waller, & Fixler, 1994). Additionally, in end-stage kidney disease, the kidneys' ability to regulate blood pressure and the body balance of many hormones is disturbed (Jalanko, 2009). Although dialysis is readily initiated, dialysis treatment also carries the risks for hypo- and hypertension, seizures, and encephalopathy. The control of blood volume and blood pressure is particularly difficult in the youngest patients (Laakkonen, 2011).

1.1.3 Liver failure

The most common indications for liver Tx in children are structural defects, especially biliary atresia (i.e., the absence or under-development of biliary tracts), congenital metabolic diseases (e.g., Wilson's disease, hyperoxaluria), hepatic malignancy, or infectious cause (hepatitis) (Fine et al., 2007; Harjula & Höckerstedt, 1995). The single most common disease leading to pediatric liver Tx worldwide is biliary atresia. Correction of biliary atresia requires early surgical correction to provide biliary drainage. Despite this measure, most children develop liver cirrhosis and liver failure (Fine et al., 2007).

In end-stage liver disease, the liver's ability to degrade cerebrotoxic substances in the blood, such as ammonia, fails. The accumulation of these toxic substances may lead to hepatic encephalopathy (Stewart et al., 1994), which resembles uremic encephalopathy. Also, malnutrition remains a problem despite nutritional support (van Mourik et al., 2000). Early Tx is often the only option to avoid permanent brain damage.

1.2 Cognitive outcome after transplantation and its risk factors

In school-aged children with an organ Tx, studies have reported intelligence in the low-average to average range compared to test norms (Adebäck, Nemeth, & Fischler, 2003; Falger et al., 2008; Kaller et al., 2005; Krull, Fuchs, Yurk, Boone, & Alonso, 2003; Qvist et al., 2002; Yssaad-Fesselier et al., 2009). Studies using a matched control group have found significantly lower intelligence than in healthy children (Brouhard et al., 2000; Wray & Radley-Smith, 2005). Most studies in the field of pediatric Tx have assessed only global intelligence. Some studies have assessed one or a few other neuropsychological functions, but comprehensive evaluations in the same patients are rare. The results have been somewhat varied and are presented below, with a focus on school-aged children and the most recent findings.

1.2.1 Heart transplantation

A majority of studies on heart Tx children come from two research groups. The research findings from Harefield Hospital (U.K.) consistently report outcome in developmental and intelligence tests within average range among patients with heart or heart-lung Tx according to test norms, but lower when compared to a healthy control group (Wray, Pot-Mees, Zeitlin, Radley-Smith, & Yacoub, 1994; Wray, Long, Radley-Smith, & Yacoub, 2001; Wray & Radley-Smith, 2005; Wray & Radley-Smith, 2006). However, researchers have suggested that the test norms of the British Ability Scales are outdated with healthy children achieving scores higher than average; thus, the statement that the Tx groups perform within average may be too optimistic (Wray et al., 2001). In the areas covered by the British Ability Scales, specific impairments emerged at school-age in short-term memory, nonverbal reasoning, and speed of information processing, compared to a control group (Wray et al., 1994).

Research findings from Loma Linda University Children's Hospital (U.S.A.) demonstrate average mental development and mildly delayed motor development in infants with Tx, when compared to test norms (Freier et al., 2004). In older children and adolescents, intelligence, expressive and receptive language, and visuomotor integration were in the borderline range (Baum et al., 2004; Krishnamurthy, Freier Randall, & Chinnock, 2011). The Loma Linda studies focus on children transplanted before the age of one year. Because of stringent exclusion criteria, nearly half of the sample was excluded, meaning that the results presented may represent a best-case scenario of infant heart Tx (Baum et al., 2004). Nearly identical results have been reported in a multicenter study that included the Loma Linda Hospital (Mahle et al., 2006). Similarly, other studies of school-aged children report specific neuropsychological impairments in expressive and receptive language (Fleisher et al., 2002) and in visuomotor and fine motor functions (Uzark, Spicer, & Beebe, 2009).

Studies on the longitudinal effect of heart Tx in school-aged children have found no changes over time when assessing cognitive and academic skills one, two (Wray et al., 2001; Wray & Radley-Smith, 2005), or three years post-Tx (Wray et al., 2001), thus indicating stability over time. For a small group of younger children (aged ≤ 3.5 years), however, a significant decrease was observed in hand-eye coordination and in the

overall developmental quotient in the first years after Tx (Freier et al., 2004; Wray & Radley-Smith, 2005) and among school-aged children in arithmetic between one and three years post-Tx (Wray & Radley-Smith, 2006). Risk factors for poorer cognitive outcome include longer waiting time for Tx (Ikle, Hale, Fashaw, Boucek, & Rosenberg, 2003), cardiopulmonary bypass time (Baum et al., 2004), number of serious infections and surgical procedures post-Tx (Baum et al., 2004), and prolonged hospitalization (Baum et al., 2004; Mahle et al., 2006). However, other studies have found no associations between the aforementioned variables and cognitive outcome (Baum et al., 1993; Brosig, Hintermeyer, Zlotocha, Behrens, & Mao, 2006). Overall, one factor places the children at risk for later cognitive deficits, and that factor is decreased oxygenation, due to both chronic heart disease and repair surgeries (Todaro, Fennell, Sears, Rodrigue, & Roche, 2000).

1.2.2 Kidney transplantation

Three studies have compared the performance of kidney Tx children to a matched control group. In an early study, Fennel and colleagues (1984) found greater improvement in performance intelligence (PIQ) and math in the kidney Tx group than in the healthy control group in assessments undertaken before the initiation of dialysis and one month post-kidney Tx; the kidney Tx children reached at that point the level of the control group. In verbal intelligence (VIQ), however, both groups had similar scores at each assessment. Additionally, no differences were found between groups at one year post-kidney Tx in measures of intelligence, achievement, problem solving, verbal memory, or attention. However, the groups were matched for intelligence, which explains their similar cognitive level (Fennell, Rasbury, Fennell, & Morris, 1984). Later, a multicenter study found significantly poorer performance on measures of nonverbal intelligence and achievement (spelling, reading, and arithmetic) in kidney Tx children than in their siblings (Brouhard et al., 2000). Another study found significant improvement in developmental/intelligence level, from borderline to low-average range, in a one-year follow-up of children with chronic kidney disease who received kidney Tx compared to children with chronic kidney disease who did not receive Tx (Icard, Hooper, Gipson, & Ferris, 2010).

Two later studies compared cognitive functions in kidney Tx children to normative data from test norms. Falger and colleagues (2008) found impairment in PIQ and motor performance (Falger et al., 2008). A study of the first kidney Tx children at the Childrens's Hospital in Helsinki reported intelligence in the low-average range. Group-level performance in neuropsychological assessment was within average in attention and executive functions, language, visuospatial processing, and memory and learning; however, 24%, 6%, 24%, and 20% of the patients, respectively, performed at or below the borderline level (Qvist et al., 2002).

Early studies associated poorer cognitive outcome with the risk factors of early onset of kidney disease (Fennell et al., 1984; Lawry, Brouhard, & Cunningham, 1994) and longer disease duration prior to Tx (Fennell et al., 1984). In more recent studies, however, cognitive impairment has been associated with neurological comorbidity (Falger et al., 2008), hypertensive crises and seizures during dialysis (Qvist et al., 2002), and lower socioeconomic status (Falger et al., 2008). Thus, early Tx may alleviate the effects of early onset of kidney disease, yet longer disease duration prior to Tx and hemodynamic changes remain risk factors for cognitive impairment.

1.2.3 Liver transplantation

In a large multicenter study, five- to seven-year-old liver Tx recipients had a group mean of average intelligence, but as many as 26% performed in the borderline range, and 4%, significantly below average (Sorensen et al., 2011). Compared to normative data, specific neuropsychological impairments in school-aged patients have been reported in expressive and receptive language (Krull et al., 2003), visuospatial performance (Stewart et al., 1991; Yssaad-Fesselier et al., 2009), sequential processing of information (Schulz, Wein, Boeck, Rogiers, & Burdelski, 2003), working memory (Kaller, Langguth, Ganschow, Nashan, & Schulz, 2010; Yssaad-Fesselier et al., 2009), and sustained attention (Kaller, Langguth et al., 2010).

The most comprehensive neuropsychological assessments to date, and the only ones who used a control group, have compared the performance of liver Tx recipients to that of another patient group with early onset of a disease thought not to affect cognitive development, namely, cystic fibrosis (Krull et al., 2003; Stewart et al., 1991). The

results are contradictory. The earlier study by Stewart and colleagues (Stewart et al., 1991) found predominantly nonverbal deficits, and the more recent one, by Krull and colleagues (Krull et al., 2003), language deficits. The study by Krull and colleagues included a patient sample with more severe disease, who received a transplant at a younger age.

In the light of studies over the past 15 years, poorer cognitive outcome may be associated mainly with the pre-Tx risk factors of longer disease duration (Kaller et al., 2005; Kaller, Langguth et al., 2010; Schulz et al., 2003), poorer physical development, and malnutrition (Gilmour, Adkins, Liddell, Jhangri, & Robertson, 2009; Kaller et al., 2005; Schulz et al., 2003; Wayman, Cox, & Esquivel, 1997), as well as health status post-Tx (Krull et al., 2003; Wayman et al., 1997). Most studies have found no relationship between follow-up time since liver Tx and cognitive outcome for follow-up times of one to ten years (Adebäck et al., 2003; Kaller et al., 2005; Kaller et al., 2010; Krull et al., 2003). However, cognitive performance may deteriorate shortly after Tx to improve in the long term to its pre-Tx level (van Mourik et al., 2000; Wayman et al., 1997). Thus, in liver Tx children, longer disease duration before Tx, with its deleterious effect on nutritional status and growth, remains a significant risk factor for cognitive development.

To summarize, the literature on cognitive outcome after pediatric organ Tx is growing, yet these studies have some inherent limitations. With regard to assessment methods, most studies assessed global intelligence only, and less is known about specific neuropsychological effects. Evaluation methods developed for toddlers have seen frequent use, yet these methods rely heavily on motor skills, and their predictive value is not great (Hack et al., 2005; Wray & Radley-Smith, 2006). The use of assessment methods for toddlers and older children, as well as different versions of the same tests within the same study further limit generalizability. Test results have generally been compared to test norms with only a few studies that included a control group.

With regard to patient samples, several successive studies have investigated the same children, which may lead to a more homogeneous picture of the population than is actually true. Only a few studies report results from the whole patient population.

Many studies have used exclusion criteria such as cognitive delay (Kaller et al., 2005; Kaller et al., 2010; Mendley & Zelko, 1999), prematurity (Stewart et al., 1991; Wayman et al., 1997), seizures (Fennell et al., 1990), changes evident on brain-magnetic resonance imaging (Kennard et al., 1999; Stewart et al., 1991), and other neurological or psychiatric conditions/sequelae (Baum et al., 2004; Brouhard et al., 2000; Krull et al., 2003; Wray et al., 1994). Differences in inclusion criteria, sample size, diagnostic groups, ages at onset of disease and at Tx, follow-up times, and assessment methods may well have affected the results between studies. Early patient cohorts also differ from more recent ones. Owing to advances in medical care, patients today have more promising outcomes than did early patient cohorts, yet more demanding patients are accepted for Tx, leading to a possible increase in neurological comorbidity. The varying use of neurodevelopmental delay as a listing criterion may further influence outcomes between centers (Richards, Crawley, & Magnus, 2009).

Evaluation of the cognitive profile of Tx children requires a comprehensive assessment of intelligence and specific neuropsychological functions in the same patient sample without excluding patients with neurological comorbidity or risk factors. A measure designed for a wide age-range enables the assessment of all children with the same measure. Including a control group is also important. Using another patient group as a control group facilitates the distinction between disease-specific cognitive deficits and those caused by childhood chronic disease per se. At school entry, however, children are compared to peers of the same age. Consequently, the use of a healthy age-matched control group sheds light on cognitive functioning in relation to age-expectations.

1.3 Behavioral outcome after organ transplantation

For a child with end-stage organ failure, Tx significantly improves wellbeing (LaRosa et al., 2011; Taylor, Franck, Gibson, & Dhawan, 2005). Even so, the level of HRQOL and PSA after Tx has been lower than that reported in the general population and similar to that of children with other chronic diseases (Alonso et al., 2010; Limbers et al., 2011; Shemesh et al., 2005). The concept of HRQOL comprises those aspects of

physical, mental, and social wellbeing that are affected by health. PSA comprises behavioral, emotional, and social functioning.

Comparisons of different pediatric solid organ Tx groups have been suggested (Fine et al., 2004), but few studies exist. Similar HRQOL and PSA have been reported in kidney and liver Tx recipients (Limbers et al., 2011; Wu, Aylward, Steele, Maikranz, & Dreyer, 2008). However, more at-risk scores in PSA emerged in self-reports of liver Tx than in those of kidney Tx recipients (Wu et al., 2008). Two research groups have recently reported studies comparing adolescents with a heart, kidney, and liver Tx. In the first study of post-traumatic stress symptoms in Tx patients and their parents, the authors hypothesized that the type of transplant with its associated prognosis and risk of mortality would predict symptoms in both patients and their parents, with the fewest symptoms after kidney and the most after heart Tx. Yet, they detected no group differences (Mintzer et al., 2005; Young et al., 2003). The second study with both cross-sectional and prospective data found no group differences in HRQOL (Devine, Reed-Knight, Simons, Mee, & Blount, 2010; Devine et al., 2011; Simons et al., 2008). In their prospective study, however, self-reports of heart Tx recipients revealed better mental health than did those of liver Tx recipients at the 18-month follow-up, but the difference did not remain after controlling for baseline mental health (Devine et al., 2011). However, results differed depending on whether they were obtained from the children or their caregivers (Devine et al., 2010; Simons et al., 2008; Wu et al., 2008), which represents a general finding (Achenbach, Dumenci, & Rescorla, 2002; Eiser & Morse, 2001). At the Childrens's Hospital in Helsinki, a comparison study between the first children receiving a heart, kidney, or liver Tx revealed no differences in HRQOL utility scores between Tx groups, except for greater discomfort in kidney Tx preadolescents and the lowest level of satisfaction with appearances in liver Tx adolescents. Further, a discrepancy was found between age groups; preadolescents reported lower HRQOL than did adolescent patients (Apajasalo et al., 1997).

Comparison studies between heart, kidney, and liver Tx children have not included a comprehensive evaluation of childhood psychopathologies assessed with a PSA questionnaire. Similarly, teacher-reports are rare. Since reports indicate problems in social and school function (Alonso et al., 2010; Qvist et al., 2004; Wray & Radley-

Smith, 2007), knowing teachers' views on how Tx children function behaviorally and socially in the class room is important.

1.3.1 Risk factors for behavioral outcome

Risk factors associated with post-Tx HRQOL and PSA in children are numerous and vary between studies depending in large part on different assessment methods, various inclusion criteria, different age groups, and the risk factors under study. Medical risk factors (i.e., neurological comorbidity, medication side-effects, secondary disease, adherence, or rejection episodes), personal factors (i.e., psychiatric history, low self-esteem, or emotional state), and family-related factors (i.e., family conflict, parental income, mother's distress, or parental physical functioning) have been associated with behavioral outcome (Devine et al., 2011; Qvist et al., 2004; Simons et al., 2008; Taylor, Franck, Gibson, Donaldson, & Dhawan, 2009; Wray & Radley-Smith, 2007). Some reports have found that psychological (i.e., family functioning, mother's distress, or pre-Tx PSA) rather than medical risk factors are important for psychological functioning after pediatric Tx (DeMaso, Douglas Kelley, Bastardi, O'Brien, & Blume, 2004; Wray & Radley-Smith, 2007).

Factors known to predict psychological difficulties among Finnish children in the general population include a history of psychopathology, parental education, family structure, family functioning, and parental wellbeing (Almqvist et al., 1999; Sourander et al., 2006). Psychiatric history, family functioning, and parental wellbeing have also been associated with outcome after Tx (DeMaso et al., 2004; Taylor et al., 2009; Wray & Radley-Smith, 2007), while results on parental income have been inconclusive (Devine et al., 2011). Marital status (married vs. not married) has shown no association with outcome after Tx (Devine et al., 2010; Simons et al., 2008); family structure (living with both biological parents), however, has a greater impact on a child's everyday life, and studying its association with outcome after Tx has recently been suggested (Denny et al., 2012; Fredericks, 2012). More information on childhood HRQOL and PSA, as well as on risk factors for poorer outcome is therefore needed to plan interventions to improve long-term outcome after pediatric Tx.

2 AIMS OF THE STUDY

This thesis addressed cognitive and behavioral outcome in school-aged children who have undergone a heart, kidney, or liver Tx. In addition, this thesis analyzed medical, neurological, and social risk factors for poorer outcome.

Studies I-III aimed to provide a comprehensive neuropsychological profile of children with a heart, kidney, or liver Tx. A series of standardized psychological tests served to assess global intelligence, attention, language, sensorimotor and visuospatial functions, memory and learning, and social processing. Additionally, parents completed a questionnaire on their child's development.

Study IV aimed to evaluate self-reported HRQOL and PSA in pediatric organ Tx recipients. Additionally, parents and teachers completed a questionnaire on the child's PSA.

3 METHODS

3.1 Subjects

3.1.1 The transplant group

All pediatric organ Tx in Finland are performed at the Helsinki University Central Hospital, where the pediatric Tx patients also attend annual medical follow-up. Children included in this study had undergone kidney or liver Tx at least one year or heart Tx at least three months prior to assessment, attended medical follow-up at the Helsinki University Central Hospital, were between 6.0 and 16.5 years of age (born between March 1991 and September 2003), and had Finnish or Swedish as their first language. A total of 19 heart, 59 kidney, and 22 liver Tx children across Finland met the inclusion criteria. Children with an acute clinical condition (one kidney and one liver Tx patient) or severe neurological comorbidity interfering with assessments (one kidney Tx patient) were excluded. One kidney Tx patient was unable to complete the assessments due to psychological distress. Six kidney Tx patients (8-16 years of age) declined to participate. Of these, one had neurological comorbidity, two had psychiatric comorbidity, and one had both. Three liver Tx patients in their teens (12-14 years of age) declined to participate; their medical records revealed that all had normal neurological and psychiatric outcome. All of the heart Tx patients elected to participate.

Altogether 19 heart, 50 kidney, and 18 liver Tx recipients participated in Studies I-III, yielding participation rates of 100%, 89%, and 86%, respectively. Diseases leading to heart Tx were: cardiomyopathy (n = 12; 63%) and CHD (n = 7; 37%); to kidney Tx: CNF (n = 22; 44%), polycystic kidneys (n = 5; 10%), renal dysplasia (n = 4; 8%), urethral valve (n = 4; 8%), and other diagnoses representing several individual diseases (n = 15; 30%); and to liver Tx: biliary atresia (n = 7; 39%), acute hepatitis (n = 3; 17%), and other diagnoses (n = 8; 44%). The patients received their transplants between 1993 and 2008. All kidney Tx children had received dialysis prior to Tx (2 hemodialysis, 46 peritoneal dialysis, and 2 both). Five patients had undergone a re-Tx: two kidney Tx children (4 and 13 years post-Tx) and one liver Tx child (1 month post-Tx). Two patients who had first received a kidney Tx later underwent a combined liver-

kidney Tx (2 and 6 years post-Tx). Information from the first Tx served as background variables, with the exception of follow-up time (second Tx), total time on dialysis, and waiting time (first + second Tx). Thus, the study assessed important risk factors (i.e., Tx at an early age, long waiting time, and short follow-up time) suggested in the existing literature. Disease duration, however, refers only to the first Tx, since the medical records were usually ambiguous about when disease recurred. In total, five patients received a combined liver-kidney Tx and one patient a combined heart-lung Tx. All liver Tx and 39 (78%) kidney Tx patients received a deceased donor's organ. Detailed characteristics of the patients appear in Table 1. Despite the Tx of different organs, the patients had received similar treatment (e.g., triple therapy immuno-suppression with cytokine inhibitors [cyclosporine or tacrolimus], antimetabolites [azathioprine or mycophenolate mofetil], and steroids [methylprednisolone]) at the same center.

Children who underwent complete neuropsychological assessment in Studies I-III were recruited to Study IV. Because of differences in study designs, the inclusion criteria differed slightly. Because Study IV compared Tx groups, it excluded children who received a combined liver-kidney Tx (n = 5 in Study II and n = 4 in Study III). Additionally, two children in Study I were assessed less than six months (3 months and 5 months) after heart Tx. To achieve more uniform inclusion criteria between Tx groups, these children were excluded from Study IV. Further, one heart and one kidney Tx patient declined to participate. Thus, a total of 74 eligible Tx patients (16 heart, 44 kidney, 14 liver) participated in Study IV.

In Studies I-III, one kidney Tx child exceeded the age criteria for the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; Wechsler, 1999), and one patient in each Tx group declined to undergo neuropsychological assessment with the NEPSY-II: A Developmental Neuropsychological Assessment (NEPSY-II; Korkman, Kirk, & Kemp, 2008). Of the 82 patients between 5 and 15 years of age, 17 heart (94%), 38 kidney (81%), and 15 liver (88%) Tx patients returned the parental evaluation of developmental problems with the Five to Fifteen questionnaire (Korkman et al., 2005). Of the 74 participants in Study IV, 66 (89%) completed a 15D-17D HRQOL self-assessment. Altogether 70 parents (95%), 35 of 42 patients over 10 years of age (no self-assessment was available for younger children; 83%), and 61 of 72 eligible

teachers (85%) completed questionnaires on the patients' PSA. Of the parents, 65 mothers (88%) and 62 fathers (84%) completed the HRQOL self-assessment. Some subjects lacked assessment of parental HRQOL; consequently, regression analyses of PSA included 57 parent reports, 30 youth reports, and 50 teacher-reports. Regression analyses of HRQOL included 65 patients. No significant differences in the participation rates emerged in HRQOL and PSA assessments between the Tx groups.

3.1.2 The control group for neuropsychological assessment

A control group was formed for each Tx group from a large standardization sample in which 923 Finnish children aged 3 to 15 years were assessed individually with NEPSY-II (Korkman et al., 2008). Data were collected during the years 2007 and 2008. These children underwent no WISC-III evaluation and completed no questionnaires. For each child with Tx, one index child of the same gender, age (within 6 months), and mother's level of education (four levels: comprehensive school, secondary level, lower and higher tertiary level) was randomly chosen. Education was classified according to the United Nations Educational, Scientific and Cultural Organization International Standard of Education, which has been applied for Finnish conditions (Official Statistics of Finland, 1997). In the standardization project, older children were assessed every second year; consequently, the sample comprised children aged 9 ± 2 months, 11 ± 2 months, 13 ± 2 months, and 15 ± 2 months. Therefore, no matches were found based on age in seven heart, seven kidney, and two liver Tx children, and the groups were treated as a group rather than as individual case-by-case matches.

The Tx groups and their respective control groups were comparable with respect to age ($p = .989$ for heart, $p = .829$ for kidney, $p = .904$ for liver Tx). Equal numbers of girls and boys were included. Similarly, mother's level of education was matched in all groups, except for one heart Tx patient for whom no index child could be found to match the mother's education. Although not a matching criterion, father's level of education did not differ between the groups ($p = .136$ for heart, $p = .053$ for kidney, $p = .423$ for liver Tx). The kidney Tx group revealed a trend toward lower education level among fathers compared to the control group.

Table 1. Background characteristics for the 87 transplant patients who participated in the study

	Heart (*n* = 19)	**Kidney** (*n* = 50)	**Liver** (*n* = 18)	**p**
Demographic and social data				
Gender:				.375[a]
male, *n* (%)	8 (42%)	28 (56%)	7 (39%)	
female, *n* (%)	11 (58%)	22 (44%)	11 (61%)	
Mother's education, *n* (%)[b]				.515[a]
Lower and higher secondary	12 (67%)	33 (67%)	14 (82%)	
Lower and higher tertiary	6 (33%)	16 (33%)	3 (18%)	
Father's education, *n* (%)[b]				.682[a]
Lower and higher secondary	12 (67%)	30 (73%)	12 (80%)	
Lower and higher tertiary	6 (33%)	11 (27%)	3 (20%)	
Child not living with both biological parents, *n* (%)[c]	2 (13%)	15 (36%)	5 (38%)	.219[a]
Pre-transplantation data				
Premature birth, gestational week < 37	2 (11%)	16 (38%)	4 (27%)	.120[a]
Congenital disease, *n* (%)	11 (61%)	46 (92%)	13 (72%)	.010[a]
Age at inclusion on the waiting list for Tx, years	5.8 ± 4.1 0.8–15.3	2.9 ± 3.4 0.4–13.0	3.9 ± 4.6 0.0–14.2	.008[d]
Waiting time for Tx, days	223.3 ± 420.7 4.0–1762.0	290.5 ± 269.4 17.0–1067.0	102.4 ± 118.1 1.0–395.0	.001[d]
Disease duration prior to Tx, years	4.2 ± 4.1 0.06–15.3	3.3 ± 2.8 0.7–10.7	2.2 ± 3.4 0.01–12.8	.005[d]
Transplantation data				
Age at first Tx, years	6.4 ± 4.3 1.0–15.3	3.7 ± 3.5 0.7–13.4	4.3 ± 4.4 0.7–14.4	.027[d]
Hospital stay after Tx, days	33.7 ± 9.6 22.0–64.0	30.9 ± 11.9 18.0–64.0	42.5 ± 18.1 23.0–99.0	.002[d]
ICU stay after Tx, days	8.9 ± 5.6 2.0–22.0	2.3 ± 0.8 1.0–5.0	5.4 ± 3.3 2.0–15.0	< .001[d]
Height at Tx, z-score[e]	-1.1 ± 1.5 -4.1–0.6	-1.6 ± 1.6 -9.0–0.7	-1.4 ± 1.8 -4.3–2.2	.366[d]

Data at the time of assessment				
Age at assessment, years	12.0 ± 3.1	1.1 ± 3.2	11.8 ± 3.1	.530[d]
	6.4–16.4	6.3–16.4	7.2–16.1	
Follow-up time from the last	5.5 ± 3.6	6.9 ± 3.6	7.6 ± 4.5	.243[f]
Tx, years	0.3–11.1	1.0–14.1	1.0–15.0	
Height at assessment, z-score[e]	-0.9 ± 1.1	-1.3 ± 1.1	-0.7 ± 1.1	.086[f]
	-3.3–0.6	-4.2–1.3	-3.4–0.8	
Neurological comorbidity, *n* (%)	7 (37%)	17 (34%)	7 (39%)	.749[a]
Psychiatric diagnosis, *n* (%)[c]	3 (19%)	11 (25%)	5 (36%)	.615[a]
Immunosuppression:				
cyclosporine, *n* (%)	15 (79%)	24 (48%)	13 (72%)	.029[a]
tacrolimus, *n* (%)	4 (21%)	26 (52%)	5 (28%)	
Mother's HRQOL score[g]	.96 ± .04	.94 ± .06	.95 ± .05	.577[d]
	.86–1.0	.77–1.0	.86–1.0	
Father's HRQOL score[g]	.94 ± .05	.97 ± .03	.97 ± .03	.074[d]
	.87–1.0	.86–1.0	.92–1.0	

HRQOL, health-related quality of life; ICU, intensive care unit; Tx, transplantation.

Note. Data presented as mean ± standard deviation and range, unless otherwise specified. Four children with a combined liver-kidney Tx are included in both the kidney and liver groups. Some information was missing for one liver Tx child who underwent Tx abroad. Due to more stringent inclusion criteria in Study IV, the patient groups were smaller than in Studies I-III. The results remained the same, however, except for two variables. Height at assessment ($p = .013$) became significant, with kidney Tx children being significantly shorter than liver Tx children ($p = .027$). Additionally, age at Tx became non-significant ($p = .102$). The direction of the results was the same, however.

[a]Exact χ^2-test

[b]Only children who had undergone neuropsychological assessment with the NEPSY-II were included. Information on the father's education was missing for eight kidney and two liver Tx children.

[c]Only children participating in Study IV were included. Information on family structure lacked for two kidney and one liver Tx children.

[d]Kruskal-Wallis test

[e]z-score = (observed height − mean height for age) / standard deviation (Pere, 2000). When children who had undergone growth hormone treatment after Tx ($n = 16$) were excluded from the analysis of height at assessment, the results remained consistent.

[f]Analysis of variance

[g]Only children participating in Study IV were included. A lower HRQOL score indicates more problems.

All children in the control group attended school with a normal curriculum, and none had any neurological diagnoses. All spoke Finnish as their first language, whereas nine children in the Tx group spoke Swedish as their first language or were bilingual Finnish-Swedish speakers and were assessed in Swedish. Analyses were performed with and without the results of these nine children. Because the results did not change, the results for these children were kept in the final analyses.

3.2 Cognitive and behavioral outcome variables

The psychological assessments used in this study appear in Table 2. A shortened version of the Finnish WISC-III (Wechsler, 1999) was used to evaluate global intelligence (WISC-IV was unavailable in Finnish). Specific subtests were selected because they had a high correlation with VIQ and PIQ. A Full-Scale IQ (FSIQ) of 85 or above (≥ -1 standard deviation; SD) was considered an average range of performance, 70-84 (-2 SD ≤ FSIQ < -1 SD) was borderline, and below 70 (< -2 SD) was significantly below average. These cutoffs agree with the ICD-10 classification of mental retardation (IQ < 70) and are generally used in pediatric Tx research.

Specific neuropsychological assessment was undertaken with NEPSY-II (Korkman, Kirk, & Kemp, 2007a; Korkman et al., 2008), a test comprising 29 subtests in six domains of development. The present study used the Finnish standardization version of the test. According to the test manual, the selection of subtests is based on the child's age and clinical needs. In this study, ten subtests were selected to provide a comprehensive profile across all domains. According to the NEPSY-II manual, a standard score of eight or above (> -1 SD) represented an average range of performance, a standard score of six or seven (-1 SD to -1⅓ SD) was borderline, and a standard score of five or below (< -1⅓ SD) was below average (Korkman, Kirk, & Kemp, 2007b). This is a more stringent classification than the one used for WISC-III in this study.

Parents also completed the Five to Fifteen questionnaire on developmental problems (Korkman et al., 2005). Lower scores indicate better outcome. The cutoff point for significant difficulties was set according to manual instructions at ≥ 90th percentile.

Table 2. Psychological assessments used in the study

Neurocognitive tests
Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; Wechsler, 1999)
Information, Similarities, Comprehension (Verbal Intelligence Quotient)
Picture Completion, Picture Arrangement, Block Design (Performance Intelligence Quotient)
NEPSY-II (Korkman, Kirk, & Kemp, 2008)
Auditory Attention and Response Set[a] (Attention and Executive Functions domain)
Speeded Naming, Comprehension of Instructions (Language domain)
Visuomotor Precision (Sensorimotor Functions domain)
Memory for Designs, Memory for Faces, Word List Interference (Memory and Learning domain)
Design Copying, Geometric Puzzles (Visuospatial Processing domain)
Affect Recognition (Social Perception domain)
Questionnaires
Five to Fifteen (Korkman et al., 2005)
Self-reported health-related quality of life (HRQOL) questionnaire
17D for ages 8-11 (Apajasalo, Rautonen et al., 1996)
16D for ages 12-15 (Apajasalo, Sintonen et al., 1996)
15D from age 16 (Sintonen, 2001)
Achenbach System of Empirically Based Assessment (ASEBA; Achenbach & Rescorla, 2001)
Child Behavior Checklist for parents
Youth Self-Report for ages 11-16
Teacher's Report Form

[a]The Auditory Attention and Response Set is one subtest, although it yields two scores: one for Auditory Attention and another for the Auditory Attention and Response Set.

HRQOL was evaluated with the self-assessment questionnaires appropriate for age: 17D© for preadolescents ages 8-11, 16D© for adolescents ages 12-15, and 15D© for those above 15 years (Apajasalo, Rautonen et al., 1996; Apajasalo, Sintonen et al., 1996; Sintonen, 2001). The contents of the three questionnaires overlap considerably. They consist of 15-17 multiple-choice questions, each representing one health-related dimension: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion,

discomfort and symptoms, school and hobbies/usual activities, vitality, depression, distress, concentration (17D), learning and memory (17D), friends (16D-17D), appearance (16D-17D), mental function (15D-16D), and sexual activity (15D). The instruments can be used both as a profile and a single health utility index (the HRQOL score, range 0-1), which are generated using a set of population preference or utility weights. Higher scores indicate better HRQOL (1 = full health). Scores across the different dimensions vary in the general population. For children under the age of eight, the 17D questionnaire was postponed until they met the age requirements.

PSA was evaluated with the Achenbach System of Empirically Based Assessment (ASEBA®) completed by the patients themselves, their parents, and teachers (Achenbach & Rescorla, 2001). These questionnaires form eight syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior. These are compiled into three summary scores: Total Problems from all the syndrome scales, Internalizing Problems from the first three syndrome scales, and Externalizing Problems from the last two syndrome scales. All of these have a mean T-score of 50 (SD 10); lower scores indicate better PSA. Cutoff points for clinical problems were set according to manual instructions at > 90^{th} percentile or a T-score of > 63 (borderline range 84^{th}-90^{th} percentile or T 60-63) for the summary scales and at > 97^{th} percentile or T > 69 (borderline range 93^{rd}-97^{th} percentile or T 65-69) for the syndrome scales.

In addition, both the mothers and fathers completed the 15D questionnaire by assessing their own perceived health and wellbeing (Sintonen, 2001). The measurement served to ensure that the Tx groups showed no differences with respect to parental wellbeing and to analyze the effect of parental wellbeing on the child's PSA.

3.3 Background and medical variables

The parents also completed a form on background variables, which included special education services received by the child, family structure, and parental education level (Table 1). Because of small sample sizes, in risk factor analyses, parental education

was merged into two categories: lower and higher secondary education versus lower and higher tertiary education.

Information on medical variables, neurological risk factors, and psychiatric diagnosis came from the patients' medical records (Table 1). Neurological comorbidities included sensory impairment; pre- and perinatal, neurological, and neurosurgical complications; and severe post-Tx complications with possible brain insult (Table 3). These were diagnosed by a clinician either before or after Tx. This classification of neurological comorbidity was used in Studies II and IV. An additional analysis was undertaken for the liver Tx group using this same classification, because no neurological risk group analysis had been performed in Study III. In Study I, classification of neurological comorbidity was based on brain imaging findings before heart Tx. Due to significant neurological symptoms, five children underwent brain magnetic resonance imaging and one child a computed tomography scan prior to heart Tx. Two of these patients had suffered brain infarction, presenting with left-sided hemiparesis. One patient with delayed motor development and hypotonicity, who was later diagnosed with mild mental retardation and ataxia, was found to have cerebellar atrophy and changes in the white matter in the lateral ventricles. One patient suffering from seizures and headaches had a cerebellar ischemic lesion and hypertensive encephalopathy. In addition, two patients had each had a brain abscess that was successfully treated. One of them exhibited left-sided hemiparesis and seizures before treatment; later, an infarct occurred in the middle cerebral artery with ischemic changes in the external capsule that caused hemiparesis lasting one day. The symptoms of the other patient with abscess are unknown. These six patients and one patient born extremely prematurely (gestational week 25) formed the neurological risk group in Study I. Further, diagnostic subgroups within each organ Tx group were for statistical purposes categorized into two groups, based on their major diagnoses (in heart CHD vs. cardiomyopathy; in kidney CNF vs. other; in liver biliary atresia vs. other).

The following additional medical variables were recorded: bypass time during heart Tx and previous corrective heart surgeries (yes/no) in heart Tx patients, time on dialysis prior to kidney Tx, highest bilirubin level prior to liver Tx, and graft function at the time of assessment (Appendix 1). All heart and liver Tx patients exhibited normal graft function. However, all patients with a kidney Tx exhibited weakened kidney

function; 19% had values near normal (glomerular filtration rate > 60 ml/min per 1.73 m^2) and 81% below normal (glomerular filtration rate ≤ 60 ml/min per 1.73 m^2). Deteriorating kidney function in long-term follow-up is a normal finding (Ortiz et al., 2005). However, all participants exhibited stable graft function with no impact on general health. For a comparison of patients with CNF and other kidney diseases, weight and height at birth, weight at Tx, and weight at the time of assessment were also recorded. These variables have shown a decrease in children with CNF (Jalanko, 2009).

Table 3. Description of 29 children with neurological comorbidity or severe risk factors

Comorbidity / Risk factor	***n***
Pre- and perinatal	
Alcohol exposure in utero with clinical sequelae	2
Birth at very low gestational age < 32 weeks (one with hearing impairment)	2
Severe asphyxia (one born at gestational week 25, two with cerebral palsy)	3
Neurological	
Diagnosis of mental retardation	4
Hemiparesis	4
Syndromes: one unspecified involving dysmorphic features and one G-protein signaling disorder with damage to several organs	2
Epilepsy	2
Neurosurgical	
Shunt due to increased intracranial pressure and hearing impairment (one with Townes-Brocks syndrome, one idiopathic)	2
Brain abscess, successfully treated	2
Neurosurgery due to Chiari 1 malformation	1
Sensory impairment	
Severe visual impairment	1
Hearing impairment	1
Post-transplantation risks	
Hypertensive encephalopathy	2
Hypertensive crises with pulmonary edema treated at the intensive care unit	1

Note. The table shows only each patient's most severe comorbidity or risk factor. The same patients may, however, exhibit other risks as well. These were diagnosed by a clinician either before or after transplantation. One single seizure was not considered a neurological sequela.

3.4 Procedure

The children were recruited for the study during their annual visit at the Helsinki University Central Hospital or an appointment was made by telephone to assess the child at the hospital closest to the patient's home. The author and two trained undergraduate research assistants performed the neuropsychological assessments between May 2007 and September 2009. Parents received written feedback on the neuropsychological assessment. If problems were found, the family was referred to a psychologist in their hometown.

The patients and their caregivers received the questionnaires when they arrived for their appointment for the neuropsychological assessments and returned the completed questionnaires in a pre-addressed, pre-paid envelope. The questionnaires were distributed by researchers (Haavisto and Qvist) who were uninvolved in the patients' clinical care. Questionnaires were collected until December 2010.

The research plan was approved by the Ethics Committee of the Helsinki University Central Hospital in April 2007. Written consent was obtained from one caregiver of each child. Additionally, children aged 15 and older provided their own written consent.

3.5 Statistical analyses

Statistical calculations were carried out using IBM SPSS Statistics 18.0.3 software. Graphical histograms and the Kolmogorov-Smirnov test of normality were used to analyze whether any variables deviated from a normal distribution. Background variables between two groups were compared using the independent samples *t*-test for normally distributed continuous variables and the Mann-Whitney *U*-test for non-normal distributions. Background variables between three groups were compared using analysis of variance (ANOVA) for normally distributed variables and the Kruskal-Wallis test for non-normal distributions, with Bonferroni corrected post hoc tests. An exact χ^2-test was used to compare categorical data.

In Studies I-III on cognitive outcome, WISC-III and NEPSY-II scores were in age-corrected standard scores. The WISC-III scores in each Tx group were compared to test norms with the Student's one-sample *t*-test (Wechsler, 1999). An additional analysis was undertaken to analyze within-group PIQ-VIQ discrepancies using the paired-samples *t*-test. For the NEPSY-II, missing observations (< 5%, range 0-3) were estimated with the expectation-maximization algorithm (Dempster, Laird, & Rubin, 1977). A profile analysis was carried out in each Tx group using mixed ANOVA with the group (Tx vs. control group) as the between-subjects factor, the NEPSY-II subtest as the within-subjects factor, and the subtest standard score as the dependent variable, thereby enabling comparison of the groups' neuropsychological test profiles (Tabachnick & Fidell, 2007). An additional analysis was undertaken with the Student's one-sample *t*-test to compare NEPSY-II scores to the test norms (Korkman et al., 2008). Bonferroni correction was calculated by multiplying each p-value by the number of comparisons (11). Outcome in patients with neurological comorbidity and organ-specific diagnostic subgroups was analyzed with the independent samples *t*-test for WISC-III and mixed ANOVA for NEPSY-II, as described above. An exact χ^2-test was used to compare the Five to Fifteen questionnaire percentile classes with expected values for the questionnaire norms (Korkman et al., 2005).

Risk factors for cognitive outcome were analyzed using the Pearson or Spearman correlation coefficient, as appropriate. The following variables were used in bivariate correlations with VIQ, PIQ, and NEPSY-II domain scores: parental education, congenital disease (yes/no), prematurity (< 37 weeks of gestation), disease duration, age at Tx and at assessment, follow-up time, as well as bypass time and corrective heart surgeries in heart Tx, time on dialysis and kidney function at the time of assessment in kidney Tx, and highest pre-Tx bilirubin level in liver Tx. A mixed ANOVA and the Mann-Whitney *U*-test were undertaken to analyze the effect of gender.

In Study IV on behavioral outcome, comparisons of 15D-17D HRQOL utility index scores between Tx groups were undertaken with analysis of covariance, adjusted for disease duration and follow-up time. Disease duration varied significantly between Tx groups (Table 1) and was significantly associated with PSA. Follow-up time was significantly associated with the utility index as well as theoretically considered an important modifier for outcome.

Further, the 15D-17D HRQOL questionnaire data were compared to population norm data consisting of representative, age-standardized samples of the Finnish general population collected for the questionnaire norms (n = 239 for 16D and n = 244 for 17D; Apajasalo, Rautonen et al., 1996; Apajasalo, Sintonen et al., 1996). A mixed ANOVA was undertaken with the group (Tx vs. general population) as the independent between-subjects factor, the 16D or 17D dimensions as the within-subjects factor, and the dimension scores as the dependent variable, thereby enabling comparison of the groups' HRQOL profiles. Additionally, 16D and 17D index scores were compared between preadolescent and adolescent Tx patients using the Mann-Whitney U-test.

ASEBA summary indices of PSA were in T-scores based on norms for children of the same age range and gender. Because Finnish norms were unavailable, U.S. norms were used. According to previous research, the test structure is similar between different cultures, including Finland and North America (Ivanova, Achenbach, Rescorla, Dumenci, Almqvist, Bathiche et al., 2007; Ivanova, Achenbach, Rescorla, Dumenci, Almqvist, Bilenberg et al., 2007; Ivanova, Dobrean et al., 2007). Comparisons of PSA between the Tx groups were undertaken with multivariate analysis of variance. The T-scores of the syndrome scales are truncated at a T-score of 50. In order to account for the full range of variation, raw scores were used for all analyses, adjusted for gender and age range (< 11 years vs. ≥ 11 years), as recommended in the manual instructions (Achenbach & Rescorla, 2001). Additionally, all analyses between the Tx groups were adjusted for disease duration and follow-up time.

Because no control group was available, T-scores of the PSA summary scores were compared to the questionnaire norms with the Student's one-sample t-test. Additionally, an exact χ^2-test was used to compare the summary and syndrome scale percentile classes with the expected values for the questionnaire norms (Achenbach & Rescorla, 2001). For both analyses, Bonferroni correction was calculated by multiplying each p-value by the number of comparisons.

Risk factors that have previously been associated with outcome or that were theoretically of interest were analyzed using the Pearson or Spearman correlation coefficient, as appropriate. These risk factors included gender, parental education, child not living with both biological parents (yes/no), congenital disease (yes/no), disease

duration, age at Tx and at assessment, follow-up time, neurological comorbidity (yes/no), psychiatric diagnosis (yes/no), parental HRQOL (the 15D score), height at assessment, and type of immunosuppressant (cyclosporine vs. tacrolimus). Variables that correlated significantly ($p < .05$) with one or more of the ASEBA summary scores or the HRQOL score were included in a multiple regression analysis. The absolute values for these correlations ranged between .258 and .427. Congenital disease, follow-up time, age at assessment, neurological comorbidity, psychiatric diagnosis, and child not living with both biological parents were entered as background variables for HRQOL. Disease duration, follow-up time, neurological comorbidity, psychiatric diagnosis, child not living with both biological parents, and mother's and father's HRQOL were entered as background variables for PSA. Different modeling methods were used (forward, backward, stepwise) due to multicollinearity. The results were the same, except that the background variables, which only showed a trend, were often excluded in the stepwise and forward analyses; the rest of the variables showed a stronger association with outcome. Backward analyses are presented.

All tests of significance were two-tailed ($p < .05$). Partial eta-squared (η_p^2) and R^2 served as indicators of effect size. In η_p^2, .01 represents a minimal effect, .06 a medium effect, and $\geq .14$ a large effect size (Cohen, 1988). The Bonferroni correction for multiple comparisons was used for all ANOVAs, analysis of covariance, and multivariate analysis of variance.

4 RESULTS

4.1 Cognitive outcome (Studies I-III)

4.1.1 Intelligence

The cognitive performance of the Tx groups on the WISC-III was compared to the test norms (Table 4). Mean FSIQs of the heart and kidney Tx children were significantly lower than expected, compared to the test norms, and fell in the borderline or near borderline range. As many as 42% of the heart and kidney Tx children had FSIQs in the borderline or below average range, compared to 16% in the standardization sample (Table 5). The mean VIQs of the heart and kidney Tx children were in the low-average range, and PIQs in the borderline range. Liver Tx children had FSIQ and VIQ within average, yet their PIQ was significantly lower than expected, compared to the test norms, and fell in the low-average range.

In general, Tx children tended to have lower scores in PIQ compared to VIQ ($t(18) = -1.80$, $p = .088$ for heart; $t(47) = -2.04$, $p = .047$ for kidney; $t(17) = -2.09$, $p = .052$ for liver Tx). The lowest subtest scores in all Tx groups emerged in the subtest Block Design.

Table 4. Mean values ± 1 standard deviation in the WISC-III for transplant patients compared to the test norms, with *t*- and p-values from the Student's one-sample *t*-test

IQ score	**Heart**			**Kidney**			**Liver**		
Subtest	**(*n* = 19)**	***t***	**p**	**(*n* = 49)**	***t***	**p**	**(*n* = 18)**	***t***	**p**
Verbal IQ	**89.8 ± 22.7**	**-1.97**	**.065**	**87.9 ± 21.9**	**-3.89**	**< .001**	**99.6 ± 20.6**	**-0.09**	**.928**
Information	7.5 ± 3.4	-3.15	.006	7.7 ± 3.2	-5.19	< .001	8.9 ± 3.1	-1.45	.166
Similarities	9.7 ± 3.9	-0.36	.725	8.7 ± 3.6	-2.62	.012	10.4 ± 3.8	0.50	.627
Comprehension	8.1 ± 4.1	-2.07	.053	8.2 ± 4.1	-2.97	.005	10.4 ± 4.5	0.42	.682
Performance IQ	**82.2 ± 18.9**	**-4.13**	**.001**	**81.1 ± 23.5**	**-5.58**	**< .001**	**88.9 ± 21.5**	**-2.19**	**.043**
Picture Completion	8.4 ± 3.3	-2.13	.047	8.0 ± 3.9	-3.56	.001	9.3 ± 3.6	-0.86	.404
Picture Arrangement	7.4 ± 3.3	-3.44	.003	7.2 ± 3.7	-5.25	< .001	8.8 ± 3.3	-1.56	.138
Block Design	6.8 ± 3.9	-3.55	.002	7.0 ± 3.9	-5.42	< .001	7.3 ± 3.9	-2.88	.010
Full-Scale IQ	**85.6 ± 18.8**	**-3.33**	**.004**	**83.9 ± 20.0**	**-5.58**	**< .001**	**94.0 ± 18.2**	**-1.40**	**.179**

IQ, Intelligence Quotient.

Table 5. Numbers (percentages) of transplant patients who performed in the average, borderline, and below-average range in the WISC-III and who received special education services according to parent-reports

	Heart (***n*** **= 19)**	**Kidney** (***n*** **= 49)**	**Liver** (***n*** **= 18)**
WISC-III performance			
Average IQ[a]	11 (58%)	28 (57%)	14 (78%)
Borderline IQ[a]	3 (16%)	12 (24%)	2 (11%)
Below-average IQ[a]	5 (26%)	9 (18%)	2 (11%)
PIQ < VIQ[b]	6 (32%)	17 (35%)	5 (28%)
Educational interventions			
Full-time special education[c]	3 (16%)	10 (20%)	3 (17%)
Part-time special education[c]	5 (26%)	7 (14%)	3 (17%)
Part-time special education in math[c]	3 (16%)	6 (12%)	3 (17%)

IQ, intelligence quotient; PIQ, performance IQ; VIQ, verbal IQ.

[a]In the standardization sample, 13.6% performed in the borderline range and 2.3%, below average.

[b]Number of children with PIQ ≤ 15 standard scores lower than VIQ.

[c]In Finland, 8% of comprehensive school students attend full-time special education, and 22% attend part-time special education. For 5% of students, the reason for transferring to special-education was a learning disability in mathematics.

4.1.2 Neuropsychological profile

The NEPSY-II profiles of the different Tx groups were compared to their respective matched control groups (Table 6). A 2 × 11 mixed ANOVA with group as the between-subjects factor, the NEPSY-II subtests as the within-subjects factor, and the subtest standard score as the dependent variable resulted in a significant and large main effect of group for all Tx groups ($F(1,34) = 10.92$, $p = .002$, $\eta_p^2 = .243$ for heart; $F(1,96) = 24.25$, $p < .001$, $\eta_p^2 = .202$ for kidney; $F(1,32) = 9.71$, $p = .004$, $\eta_p^2 = .233$ for liver). The test × group interaction indicated no difference in the shape of the test profiles between heart and liver Tx patients and their control groups ($F(10,340) = 1.16$, $p = .320$, $\eta_p^2 = .033$ for heart; and Greenhouse-Geisser corrected $F(7.2,231.7) = 1.41$, $p = .199$, $\eta_p^2 = .042$ for liver), but for kidney Tx children, the effect of group was not similar for all subtests (Greenhouse-Geisser corrected corrected $F(8.3,792.3) = 2.25$, $p = .021$, $\eta_p^2 = .023$). The Bonferroni corrected post hoc tests appear in Table 6. The heart Tx group had lower scores in the verbal tasks of Comprehension of Instructions and Word List Interference, the visuospatial tasks of Design Copying and Memory for Designs, and Affect Recognition. The kidney Tx group scored significantly lower than the control group across domains, except for visual memory. The liver Tx group had a specific profile of lower scores in the domains of Sensorimotor Functions, Visuospatial Processing, and Social Perception. The lowest subtest scores emerged in all Tx groups in Visuomotor Precision and Design Copying, which all fell in the borderline range.

Because the scores of the matched control groups differed from the mean of the standardization sample, an additional analysis was conducted to compare the different Tx groups with the test norms. In the heart and liver Tx groups, only Visuomotor Precision and Design Copying differed significantly from the test norms ($t(17) = -4.08$, $p = .011$ and $t(17) = -5.30$, $p < .001$ for heart Tx; and $t(16) = -3.43$, $p = .033$ and $t(16) = -3.89$, $p = .011$ for liver Tx). In the kidney Tx group, a generalized effect across domains remained. However, Auditory Attention and Response Set became non-significant, whereas Memory for Faces ($t(48) = -3.43$, $p = .011$) became significant. These results further underscore the visuomotor and visuoconstructive deficits observed in heart and liver Tx patients and the generalized effect in kidney Tx patients.

Table 6. Mean values ± 1 standard deviation in the NEPSY-II for transplant patients compared to their matched control groups, with *F*- and p-values from 2 × 11 mixed ANOVAs with Bonferroni corrected post-hoc tests

Domain	**Heart**	**Controls**			**Kidney**	**Controls**			**Liver**	**Controls**		
Subtest	**(*n* = 18)**	**(*n* = 18)**	$F_{(1,34)}$	**p**	**(*n* = 49)**	**(*n* = 49)**	$F_{(1,96)}$	**p**	**(*n* = 17)**	**(*n* = 17)**	$F_{(1,32)}$	**p**
Attention and Executive Functions												
Auditory Attention	9.9 ± 1.9	9.7 ± 2.3	0.04	.845	9.6 ± 2.8	10.4 ± 1.7	3.08	.082	9.5 ± 1.5	10.3 ± 1.5	2.28	.141
Auditory Attention and Response Set	9.2 ± 3.3	9.7 ± 2.6	0.25	.621	8.5 ± 3.9	10.1 ± 3.0	4.83	.030	8.1 ± 3.4	10.1 ± 3.7	2.64	.114
Language												
Comprehension of Instructions	8.7 ± 3.2	11.1 ± 2.4	6.54	.015	7.2 ± 3.9	10.0 ± 2.6	18.58	< .001	8.1 ± 4.4	10.5 ± 2.5	3.90	.057
Speeded Naming	8.4 ± 2.7	9.7 ± 2.1	2.35	.134	8.3 ± 3.2	10.0 ± 2.6	9.10	.003	8.8 ± 2.5	8.7 ± 2.9	0.02	.888
Sensorimotor Functions												
Visuomotor Precision	7.7 ± 2.4	9.3 ± 3.0	2.95	.095	7.3 ± 2.9	9.7 ± 2.8	18.18	< .001	7.3 ± 3.3	9.9 ± 2.7	6.33	.017
Memory and Learning												
Memory for Faces	8.9 ± 3.0	9.8 ± 3.3	0.64	.428	8.4 ± 3.3	9.1 ± 3.0	1.36	.246	9.1 ± 3.9	9.5 ± 3.1	0.12	.735
Memory for Designs	7.9 ± 3.4	10.2 ± 2.6	5.35	.027	8.8 ± 4.2	9.6 ± 3.0	1.42	.237	8.2 ± 4.0	9.7 ± 2.2	1.92	.176
Word List Interference	8.8 ± 2.8	11.1 ± 2.6	6.24	.018	8.1 ± 3.7	10.3 ± 3.2	10.06	.002	9.2 ± 4.2	11.1 ± 2.6	2.48	.126
Visuospatial Processing												
Design Copying	7.0 ± 2.4	9.6 ± 2.7	8.83	.005	6.2 ± 3.4	9.2 ± 2.9	21.34	< .001	6.5 ± 3.7	9.9 ± 2.7	9.51	.004
Geometric Puzzles	8.4 ± 3.2	10.3 ± 3.1	3.12	.087	7.9 ± 3.5	9.9 ± 2.4	10.58	.002	8.1 ± 2.9	10.6 ± 2.2	8.17	.007
Social Perception												
Affect Recognition	7.9 ± 3.9	10.3 ± 2.2	5.25	.028	8.3 ± 3.1	10.4 ± 2.1	14.99	< .001	8.5 ± 2.7	10.9 ± 1.6	9.30	.005

4.1.3 Groups with neurological risk factors

In all Tx groups, a significant minority of patients had neurological comorbidity or neuroradiological findings. To compare patients who had neurological comorbidity and those who did not, an independent samples *t*-test was undertaken for WISC-III and a 2 × 11 mixed ANOVA with group as the between-subjects factor, the NEPSY-II subtests as the within-subjects factor, and the subtest standard score as the dependent variable for NEPSY-II.

In the heart Tx group, children with neuroradiological findings pre-Tx and one child with extreme prematurity (n = 7) scored lower than did children without neurological risk factors (n = 12) on the WISC-III (VIQ 76.6 ± 11.3 vs. 97.5 ± 24.4, p = .049; PIQ 68.1 ± 18.4 vs. 90.3 ± 14.1, p = .009; and FSIQ 72.1 ± 13.4 vs. 93.5 ± 17.2, p = .012) and the NEPSY-II ($F(1,16) = 6.36$, p = .023, $\eta_p^2 = .284$). However, the low-risk group also continued to score below test norms on PIQ (p = .037) and generally lower than the control group on the NEPSY-II ($F(1,28) = 4.61$, p = .041, $\eta_p^2 = .141$). Bonferroni corrected post hoc tests revealed that the low-risk group scored lower than their matched control group on Design Copying (p = .039). Abnormalities on brain imaging were associated with the number of heart surgeries prior to Tx ($U = 17.50$, p = .016) and a diagnosis of CHD ($\chi^2(1) = 5.70$, p = .017).

In the kidney Tx group, a significant minority of children had neurological comorbidity or risk factors diagnosed by a clinician either before or after Tx (n = 17). Patients with neurological comorbidity had significantly lower scores than did children without major neurological comorbidity (n = 33) on the WISC-III (VIQ 77.1 ± 25.0 vs. 93.1 ± 18.4, p = .015; PIQ 63.9 ± 26.7 vs. 88.9 ± 17.2, p = .003; and FSIQ 69.2 ± 24.0 vs. 90.6 ± 13.7, p = .005) and the NEPSY-II ($F(1,47) = 5.16$, p = .001, $\eta_p^2 = .099$). However, children without neurological comorbidity also continued to score below test norms on the WISC-III (VIQ p = .038; PIQ p = .001; FSIQ p < .001) and generally lower than the control group on the NEPSY-II ($F(1, 77) = 8.79$, p = .004, $\eta_p^2 = .102$). Bonferroni corrected post hoc tests revealed that kidney Tx children without neurological comorbidity scored lower than their matched control group on

Comprehension of Instructions (p = .006), Design Copying (p = .007), and Affect Recognition (p = .018).

In the liver Tx group, children with neurological comorbidity or risk factors (*n* = 7), diagnosed either before or after Tx, did not differ significantly from patients without major neurological comorbidity (*n* = 11) on the WISC-III (VIQ 89.9 ± 20.7 vs. 105.7 ± 18.9, p = .113; PIQ 82.6 ± 23.9 vs. 93.0 ± 19.8, p = .329; and FSIQ 85.9 ± 21.5 vs. 99.2 ± 14.4, p = .113) or the NEPSY-II ($F(1,15) = 0.86$, p = .368, $\eta_p^2 = .054$). Children without neurological comorbidity continued to score lower than the control group on the NEPSY-II ($F(1,26) = 5.00$, p = .034, $\eta_p^2 = .161$), specifically on Visuomotor Precision (p = .043), Design Copying (p = .020), and Affect Recognition (p = .007).

4.1.4 Organ-specific diagnostic subgroups

The cognitive outcome of the major diagnostic subgroups within the Tx groups were analyzed. Because of the small group sizes, no statistically significant differences emerged. However, some interesting trends were noted. For heart Tx, children with CHD did not differ significantly from children with cardiomyopathy, but a large effect size was observed in NEPSY-II (see Table 7 for WISC-III scores; $F(1,16) = 3.05$, p = .100, $\eta_p^2 = .160$ for NEPSY-II). On average, children with CHD scored 11 points lower than children with an initial diagnosis of cardiomyopathy on FSIQ.

Similarly for kidney Tx, children with CNF did not differ significantly from children with other kidney diseases (see Table 8 for WISC-III scores; $F(1,47) = 1.72$, p = .196, $\eta_p^2 = .035$ for NEPSY-II). Because we are unaware of other studies reporting the cognitive outcome of CNF children alone, a more detailed comparison of the groups was undertaken even though the group comparisons were non-significant. A trend toward better performance in PIQ occurred in patients with CNF, which approached significance (Table 8). Similarly, Bonferroni corrected post hoc tests revealed better scores for the CNF group in Design Copying and Geometric Puzzles, and the differences approached significance (7.2 ± 2.9 vs. 5.4 ± 3.6, p = .062 and 8.9 ± 3.3 vs. 7.2 ± 3.4, p = .096, respectively). Of the non-CNF children, 86% had a congenital disease.

Table 7. Comparison of heart transplant patients with congenital heart disease (CHD) and patients with cardiomyopathy

	CHD (*n* = 7)	Cardiomyopathy (*n* = 11)	p
Pre-transplantation data			
Disease duration prior to Tx, years	7.7 ± 4.7	2.2 ± 1.7	.021
Waiting time for Tx, days	0.5 ± 0.9	0.7 ± 1.3	.761
Brain abnormality	5 (71%)	2 (29%)	.013[a]
Transplantation data			
Age at first Tx, years	7.7 ± 4.7	5.6 ± 4.1	.327
Height at Tx, z-score[b]	-1.4 ± 1.5	-0.85 ± 1.5	.422
Bypass time during Tx, min	208.9 ± 75.2	158.4 ± 64.3	.147
Data at the time of assessment			
Age, years	12.6 ± 3.1	11.9 ± 3.0	.626
Follow-up time from the last Tx, years	4.8 ± 4.7	6.0 ± 3.0	.511
Height, z-score[b]	-1.2 ± 0.9	-0.6 ± 1.1	.248
Cognitive performance			
Verbal IQ	82.4 ± 23.9	94.1 ± 21.8	.292
Performance IQ	75.7 ± 15.4	85.9 ± 20.3	.267
Full-scale IQ	78.7 ± 18.1	89.7 ± 18.7	.230

CHD, congenital heart disease; IQ, Intelligence Quotient; Tx, transplantation.

Note. Data presented as mean ± 1 standard deviation, unless otherwise specified, with p-values from the independent samples *t*-test.

[a]Exact χ^2-test

[b]z-score = (observed height − mean height for age) / standard deviation (Pere, 2000). When children who had undergone growth hormone treatment after Tx were excluded, the results remained consistent.

Table 8. Comparison of kidney transplant patients with congenital nephrosis of the Finnish type (CNF) and patients with other diagnoses

	CNF (*n* = 22)	Other (*n* = 28)	p
Birth data			
Gestational age, weeks	35.5 ± 2.3	37.4 ± 2.3	.026
Height, cm	47.2 ± 3.0	49.1 ± 2.2	.023
Birth weight, kg	2.5 ± 0.4	3.3 ± 0.6	< .001
Pre-transplantation data			
Disease duration prior to Tx, years	1.9 ± 0.9	4.3 ± 3.3	.001
Time on dialysis, years[a]	1.5 ± 1.1	1.3 ± 1.2	.670
Waiting time for Tx, days[a]	386 ± 315	223 ± 213	.060
Transplantation data			
Age at first Tx, years	1.9 ± 0.9	5.2 ± 4.1	< .001
Height at Tx, z-score[b]	-1.2 ± 2.0	-1.9 ± 1.3	.140
Weight for height index at Tx, %[c]	0.6 ± 8.5	12.5 ± 20.7	.009
Data at the time of assessment			
Age, years	11.0 ± 3.4	11.3 ± 3.1	.742
Follow-up time from the last Tx, years	8.2 ± 3.4	5.8 ± 3.5	.016
Height, z-score[b]	-0.9 ± 0.9	-1.7 ± 1.1	.010
Weight for height index, %[c]	0.6 ± 9.0	20.8 ± 35.3	.008
Neurological comorbidity, *n* (%)	7 (32%)	10 (36%)	1.000[d]
Cognitive performance			
Verbal IQ	89.3 ± 16.2	86.8 ± 25.6	.668
Performance IQ	88.6 ± 20.4	75.3 ± 24.4	.050
Full-scale IQ	88.4 ± 13.7	80.4 ± 23.5	.144

CNF, congenital nephrosis of the Finnish type; IQ, Intelligence Quotient; Tx, transplantation.

Note. Data presented as mean ± 1 standard deviation, unless otherwise specified, with p-values from the independent samples *t*-test. When children with CNF were compared in an additional analysis to children with other congenital diseases, the results remained consistent, except for three variables. Birth height (p = .073) and follow-up time (p = .061) changed from significant to nearly significant, while Performance IQ became significant (p = .032).

[a]Total time on peritoneal or hemodialysis. For patients with retransplants, time on dialysis and waiting time for Tx include both the first and second Tx.

[b]z-score = (observed height − mean height for age) / standard deviation (Pere, 2000). When children who had undergone growth hormone treatment after Tx were excluded, the results remained consistent.

[c]% = ratio of weight (kg) for height (cm) to the mean weight for height ratio in the normal population (Pere, 2000).

[d]Exact χ^2-test

Liver Tx children with an initial diagnosis of biliary atresia did not differ from those with other diagnoses. They were comparable in both the WISC-III (FSIQ 92.3 ± 19.4 in biliary atresia vs. 94.0 ± 18.8 in other diagnoses, p = .858) and the NEPSY-II test profiles ($F(1,15) = 1.12$, p = .306, $\eta_p^2 = .070$). Consequently, no comparisons of background variables were undertaken.

4.1.5 Parental evaluation of development

Five to Fifteen evaluations were compared to the questionnaire norms (Table 9). The results indicate a statistically significant increase in the frequency of various developmental and behavioral problems reported by parents of Tx children. Across Tx groups, more problems were reported in the domains of Motor Skills, Perception, Memory, and Emotional/Behavioral Problems. Heart Tx children had additionally pronounced problems in Language. Kidney Tx children had more problems across the domains. Liver Tx children had additionally more problems in Learning and Social Skills.

Table 9. Numbers (and percentages) of transplant patients with problems exceeding the cutoff point for significant difficulties (90th percentile) in the Five to Fifteen questionnaire, with χ^2- and p-values from comparisons with the expected distribution based on the questionnaire norms

	Heart			Kidney			Liver		
	(*n* = 17)	χ^2	p	(*n* = 38)	χ^2	p[a]	(*n* = 15)	χ^2	p
Motor Skills	5 (29%)	14.44	.006	14 (37%)	67.29	< .001	6 (40%)	31.30	< .001
Executive Functions	2 (12%)	4.69	.321	7 (18%)	16.38	.006	4 (27%)	8.41	.078
Perception	2 (12%)	9.59	.048	12 (32%)	34.14	< .001	5 (33%)	17.74	.001
Memory	5 (29%)	14.44	.006	17 (45%)	77.19	< .001	4 (27%)	14.24	.007
Language	6 (35%)	21.51	< .001	14 (37%)	46.49	< .001	3 (20%)	7.30	.121
Learning[b]	2 (15%)	6.32	.176	8 (31%)	32.89	< .001	3 (25%)	13.93	.008
Social Skills	3 (18%)	7.38	.117	10 (26%)	26.40	.001	6 (40%)	23.31	< .001
Emotional/Behavioral Problems	4 (24%)	10.06	.039	12 (32%)	31.18	< .001	6 (40%)	19.61	.001

Note. Expected percentages, increasing in problem severity, were 25, 50, 15, 8, and 2. Because assumptions were slightly violated, we reanalyzed the data using an exact χ^2-test. Because the exact tests are more conservative, two p-values in the heart Tx group changed from significant to nearly significant. Exact p-values were p = .066 for Perception and p = .053 for Emotional/Behavioral Problems.

[a]P-values for exact χ^2-tests are reported.

[b]Norms are provided from age nine; this includes 13 heart, 26 kidney, and 12 liver transplanted children.

4.1.6 Risk factors for cognitive outcome

The results of those background variables that correlated significantly with cognitive outcome appear in Table 10. The following background variables strongly intercorrelated: longer duration of kidney disease correlated with older age at Tx (r_s = .967, p < .001) and with shorter follow-up time after Tx (r_s = -.448, p = .001). Likewise, older age at Tx and shorter follow-up time correlated for all Tx groups (r_s = -.740, p < .001 for heart; r_s = -.485, p < .001 for kidney; and r_s = -.672, p = .002 for liver Tx).

Only a few associations emerged between risk factors and cognitive outcome after heart Tx. Intelligence showed no significant association with any of the risk factors, yet a trend for poorer PIQ emerged in children who had undergone corrective heart surgeries pre-Tx. Similarly, corrective heart surgeries showed a significant association with lower scores in Executive Functions. Lower Visuospatial Processing was associated with congenital disease (both CHD and cardiomyopathy with congenital onset) and longer follow-up time.

In kidney Tx patients, poorer kidney function showed a negative association with VIQ and Language functions, Executive Functions, as well as Memory and Learning. The highly intercorrelated variables of longer disease duration, older age at Tx and at assessment, and shorter follow-up time were also associated with cognitive outcome, particularly the IQ measures.

In liver Tx patients, congenital disease and longer disease duration were strongly associated with lower PIQ. The strongly intercorrelated variables of older age at Tx and shorter follow-up time showed a negative association with Executive Functions, Memory and Learning, and Social Processing.

Because Studies I-III did not control for gender, mixed ANOVAs were carried out for all Tx groups combined. No significant main effect of gender emerged, indicating that girls and boys had similar group mean performance ($F(1,83)$ = .021, p = .885, η_p^2 < .001 for WISC-III; $F(1,82)$ = .075, p = .785, η_p^2 = .001 for NEPSY-II). To determine whether one gender had more severe impairments, FSIQ and NEPSY-II domains that fell more than 2 SD below the test norms were counted for each child. No differences

emerged in the Mann-Whitney *U*-test, indicating that girls and boys had similar numbers of low scores ($p = .447$).

Table 10. Correlations between background variables and outcome in the WISC-III and the NEPSY-II for transplant patients

	WISC-III		NEPSY-II					
	VIQ	**PIQ**	**Executive Functions**	**Language**	**Sensorimotor Functions**	**Visuospatial Functions**	**Memory and Learning**	**Social Processing**
Heart								
Congenital disease[a]	- .188	- .376	- .276	- .201	- .393	- .615**	- .141	- .377
Corrective heart surgeries[a]	- .308	- .429[†]	- .541*	- .219	- .299	- .254	- .182	- .110
Follow-up time	- .198	- .361	- .022	- .219	- .297	- .556*	- .289	- .135
Kidney								
Disease duration	- .314*	- .290*	- .265[†]	- .152	- .329*	- .170	- .243[†]	- .215
Age at Tx	- .293*	- .253[†]	- .235	- .113	- .238	- .092	- .211	- .175
Age at assessment	- .049	- .424**	- .177	- .143	- .114	- .252[†]	- .198	- .358*
Follow-up time	.012	- .070	.045	- .089	.039	- .061	.029	- .329*
Glomerular filtration rate[b]	.390**	.200	.367*	.363*	.042	.183	.327*	.113
Serum creatinine[b]	- .287*	- .030	- .402**	- .323*	.148	.009	- .048	- .152
Liver								
Congenital disease[a]	- .181	- .603**	.197	- .110	.096	- .109	- .167	.006
Disease duration	- .111	- .850***	- .029	- .319	- .133	- .460[†]	- .386	- .203
Age at Tx	.213	- .315	- .563*	- .210	- .377	- .367	- .480[†]	- .607*
Follow-up time	- .159	.149	.526*	.197	.302	.374	.562*	.463[†]

PIQ, Performance Intelligence Quotient; Tx, transplantation; VIQ, Verbal Intelligence Quotient.

Note. Data expressed as Pearson's or Spearman's correlation coefficient, as appropriate. No significant correlations emerged between outcome and parental education, prematurity, bypass time during heart Tx, time on dialysis pre-kidney Tx, or highest bilirubin level pre-liver Tx. ***p < .001, **p < .01, *p < .05, †p < .10

[a]A point-biserial correlation was used for congenital disease, corrective heart surgeries (yes/no), and neurological comorbidity: 0 represents patients without these conditions, and 1 represents patients with these conditions.

[b]A higher glomerular filtration rate and lower serum creatinine indicate more efficient kidney function. The measurements were obtained at the time of follow-up.

4.2 Behavioral outcome (Study IV)

4.2.1 Health-related quality of life

The HRQOL of heart, kidney, or liver Tx children was compared in an analysis of covariance with the group as the between-subjects factor and the 15-17D utility score as the within-subjects factor, adjusting for disease duration and follow-up time. No statistically significant difference in HRQOL emerged between the Tx groups ($F(2,61) = 0.73$, $p = .485$, $\eta_p^2 = .023$). The mean HRQOL scores were .94 ± .05 for 13 heart, .92 ± .08 for 40 kidney, and .93 ± .07 for 13 liver Tx patients. Thus, further analyses were undertaken for all Tx groups combined.

The HRQOL profiles of the Tx groups were compared to those of the general population in a mixed ANOVA with the group as the between-subjects factor, the 16D or 17D dimensions as the within-subjects factor, and the dimension scores as the dependent variable. In 17D, the preadolescent patients (8-11 years) had a significantly lower HRQOL score than did the general population ($F(1,274) = 5.44$, $p = .020$, $\eta_p^2 = .019$). The test × group interaction indicated that the effect of group was not similar for all dimensions (Greenhouse-Geisser corrected $F(10.8,2954.6) = 3.87$, $p < .001$, $\eta_p^2 = .014$). The Tx preadolescents were worse off in the dimensions of excretion ($p < .001$), eating ($p < .001$), and their state of health made it more difficult for them to make or be with friends ($p = .002$) or to attend school and engage in hobbies ($p < .001$). In 16D, the adolescents (12-15 years) scored on the level of the general population ($F(1,270) = 0.14$, $p = .710$, $\eta_p^2 = .001$). The test × group interaction indicated that the effect of group was not similar for all dimensions (Greenhouse-Geisser corrected $F(10.0,2688.4) = 4.90$, $p < .001$, $\eta_p^2 = .018$). The Tx adolescents had significantly fewer self-reported feelings of distress ($p = .010$) and experienced more vitality ($p = .002$) than did the general population, but they also reported more problems with excretion ($p < .001$), mobility ($p < .001$), eating ($p < .001$), attending school ($p = .001$), and being with friends ($p = .004$).

Preadolescents, as a group, reported lower self-reported HRQOL than did adolescent patients (17D .91 ± .06 vs. 16D .94 ± .08, $p = .002$). Preadolescents were more likely to

have a congenital disease (91% vs. 70%, p = .030), were younger at Tx (2.5 ± 1.7 vs. 5.3 ± 4.1, p = .007), and had a shorter follow-up time (5.7 ± 2.1 vs. 8.5 ± 4.2, p < .001). Fewer preadolescents had experienced a rejection episode (59% vs. 82%, p = .032). The groups did not differ in any other background variables.

4.2.2 Psychosocial adjustment

The PSA of heart, kidney, or liver Tx children was compared in multivariate analysis of variance with the group as the between-subjects factor and the ASEBA scores of Internalizing and Externalizing Problems as the within-subjects factors, adjusting for disease duration and follow-up time. No statistically significant differences in PSA emerged between the Tx groups ($F(4,124) = 1.59$, p = .180; Wilk's $\lambda = .905$, $\eta_p^2 = .049$ for parent reports; $F(4,56) = 0.57$, p = .683; Wilk's $\lambda = .923$, $\eta_p^2 = .039$ for youth self-reports; $F(4,106) = 1.71$, p = .154; Wilk's $\lambda = .883$, $\eta_p^2 = .060$ for teacher-reports). For mean T-scores, see Table 11. Further analyses were undertaken for all Tx groups combined.

The Student's one sample *t*-test revealed significantly more parent- and teacher-reported Total and Internalizing Problems compared to the questionnaire norms (Table 12). Despite this increase, mean scores fell in the normal range; the χ^2-tests revealed an increased amount of problems in the clinically significant range only in parent-reported Total and Internalizing Problems. The increase in Internalizing Problems identified in parent reports is attributable mainly to significant Somatic Complaints in 24% of the patients. Compared to the norms, this is significantly more than expected ($\chi^2(1) = 25.23$, p < .001). Parents also reported that their children had more Social Problems ($\chi^2(2) = 14.89$, p = .02) in the borderline range than was expected from the norms. Youth self-reports did not differ from the questionnaire norms.

Parent- and self-reports showed a moderate correlation ($r = .677$, p < .001 and $r = .482$, p = .003 for Internalizing and Externalizing Problems, respectively), as did parent- and teacher-reports ($r = .451$, p < .001 and $r = .366$, p = .004). Teacher- and self-reports showed no significant correlation ($r = .159$, p = .401 and $r = -.067$, p = .724).

Table 11. Mean T-scores ± 1 standard deviation for children who have undergone a heart, kidney, or liver transplantation in the ASEBA questionnaire of psychosocial adjustment

	Parent-reported Child Behavior Checklist			**Youth Self-Report**			**Teacher's Report Form**		
	Heart (*n* = 16)	**Kidney (*n* = 41)**	**Liver (*n* = 13)**	**Heart (*n* = 10)**	**Kidney (*n* = 17)**	**Liver (*n* = 8)**	**Heart (*n* = 15)**	**Kidney (*n* = 35)**	**Liver (*n* = 11)**
Anxious/Depressed	54.1 ± 6.1	53.9 ± 5.6	56.8 ± 7.1	52.6 ± 3.7	53.8 ± 6.3	55.6 ± 7.3	57.1 ± 7.6	52.6 ± 4.3	57.0 ± 4.9
Withdrawn/Depressed	57.9 ± 8.2	55.1 ± 6.2	57.4 ± 8.7	53.4 ± 3.3	54.3 ± 6.1	53.9 ± 5.5	57.9 ± 9.2	55.3 ± 7.2	57.9 ± 5.7
Somatic Complaints	57.9 ± 7.3	55.4 ± 6.9	58.7 ± 7.0	61.1 ± 6.2	56.1 ± 6.5	55.0 ± 3.6	55.3 ± 6.5	54.3 ± 6.2	53.4 ± 6.5
Social Problems	57.9 ± 7.3	55.4 ± 6.9	58.7 ± 7.0	55.7 ± 6.7	54.6 ± 6.2	56.8 ± 6.8	58.2 ± 7.3	55.8 ± 6.4	57.0 ± 7.2
Thought Problems	54.4 ± 7.0	54.9 ± 6.3	54.9 ± 4.6	55.9 ± 6.5	52.3 ± 3.1	57.8 ± 5.6	52.3 ± 6.2	51.5 ± 3.5	51.5 ± 3.2
Attention Problems	56.6 ± 7.2	56.2 ± 6.6	57.5 ± 7.2	54.6 ± 4.1	57.1 ± 7.1	57.5 ± 8.0	58.7 ± 6.2	53.6 ± 3.8	60.3 ± 5.8
Rule-Breaking Behavior	53.5 ± 6.0	54.1 ± 5.9	57.4 ± 6.2	53.1 ± 3.1	55.4 ± 6.6	55.0 ± 4.8	51.5 ± 3.3	52.4 ± 3.8	54.6 ± 5.5
Aggressive Behavior	55.6 ± 6.6	55.5 ± 8.7	56.3 ± 6.6	52.8 ± 3.4	55.3 ± 6.7	54.8 ± 6.8	54.3 ± 5.7	53.1 ± 4.8	55.5 ± 8.4
Internalizing Problems	**57.6 ± 8.8**	**53.6 ± 11.0**	**58.8 ± 10.2**	**53.9 ± 6.4**	**49.9 ± 11.3**	**52.0 ± 10.1**	**56.6 ± 10.1**	**50.4 ± 9.1**	**57.5 ± 5.6**
Externalizing Problems	**51.8 ± 9.8**	**50.6 ± 10.8**	**55.8 ± 7.8**	**50.3 ± 5.3**	**51.8 ± 10.8**	**52.9 ± 7.7**	**51.7 ± 7.6**	**49.7 ± 7.4**	**53.6 ± 9.5**
Total Problems	**54.8 ± 9.8**	**51.9 ± 11.1**	**57.5 ± 8.6**	**52.2 ± 7.0**	**51.4 ± 9.6**	**54.3 ± 8.5**	**57.9 ± 5.9**	**51.9 ± 5.9**	**57.9 ± 8.1**

ASEBA, The Achenbach System of Empirically Based Assessment.

Note. The ASEBA questionnaires have a mean of 50 (standard deviation = 10). A lower score indicates better psychosocial adjustment. The cutoff point for clinical problems in the syndrome scales is T > 69 (> 97th percentile) and in the summary scores, presented in bold, T > 63 (> 90th percentile).

Table 12. Mean T-scores ± 1 standard deviation on psychosocial adjustment for transplant patients compared to the ASEBA questionnaire norms, with *t*- and p-values from the Student's one-sample *t*-test, as well as numbers (percentages) exceeding the cutoff for clinical problems, with χ^2- and p-values from comparisons with the expected distribution based on the questionnaire norms

	T-score	*t*	p	Clinical problems	χ^2	p[a]
Parent-reported Child Behavior Checklist (*n* = 70)						
Internalizing Problems	55.5 ± 10.5	4.34	< .001	20 (29%)	26.83	< .001
Externalizing Problems	51.8 ± 10.1	1.51	.136	11 (16%)	2.54	.158
Total Problems	53.6 ± 10.5	2.89	.015	15 (21%)	10.16	.009
Youth Self-Report (*n* = 35)						
Internalizing Problems	51.5 ± 9.8	0.92	.365	4 (11%)	0.08	1.000
Externalizing Problems	51.6 ± 8.7	1.09	.283	4 (11%)	0.08	1.000
Total Problems	52.3 ± 8.5	1.56	.127	4 (11%)	0.08	1.000
Teacher Report Form (*n* = 61)						
Internalizing Problems	53.2 ± 9.3	2.68	.027	7 (11%)	0.15	.831
Externalizing Problems	50.9 ± 7.9	0.85	.400	3 (5%)	1.75	.209
Total Problems	54.5 ± 6.9	5.06	< .001	3 (5%)	1.75	.209

ASEBA, The Achenbach System of Empirically Based Assessment.

Note. The ASEBA questionnaires have a mean of 50 (standard deviation = 10). A lower score indicates better psychosocial adjustment. The cutoff point for clinical problems is T > 63 (> 90th percentile).

[a]P-values for exact χ^2-tests are reported.

4.2.3 Risk factors for behavioral outcome

Since no significant differences between the Tx groups emerged, regression analyses were conducted for all Tx groups combined. For the self-reported HRQOL utility score, shorter follow-up time, acquired disease, psychiatric diagnosis, and neurological comorbidity accounted for 34% of the variance (Table 13). Risk factors associated with PSA differed depending on the rater (Table 14). PSA problems were associated with neurological comorbidity, parental HRQOL, family structure, and shorter follow-up time. Additionally, in teacher-reports, longer disease duration was associated with poorer PSA. Overall, associations between PSA and background variables were not high, especially not for self-reports.

The most impaired syndrome scale, namely parent-reported Somatic Complaints, was analyzed separately; it was associated with shorter follow-up time (adjusted R^2 = .086, p = .014).

Table 13. Multiple regression analysis of variables associated with self-reported health-related quality of life (15D-17D scores)

Variable	B	95% CI for B	β	Adjusted R^2
				.340
Follow-up time	0.007	0.003, 0.011	.363**	
Psychiatric diagnosis[a]	-0.059	-0.094, -0.024	-.355**	
Congenital disease[a]	-0.053	-0.090, -0.015	-.308**	
Neurological comorbidity[a]	-0.028	-0.060, -0.004	-.186†	

Note. The model excluded the non-significant variables child not living with both parents and age at assessment. The analyses included 65 patients. A lower score in the 15D-17D questionnaires indicates more problems. **p < .01, *p < .05, †p < .10

[a]Congenital disease, neurological comorbidity, and psychiatric diagnosis were coded as dichotomous variables. In all cases, 0 represents patients without a congenital disease and patients without neurological or psychiatric comorbidity; 1 represents the presence of these risk factors.

Table 14. Multiple regression analyses of variables associated with psychosocial outcome in the ASEBA questionnaires

	Variable	B	95% CI for B	β	Adjusted R^2
Total Problems	**Parent-reported Child Behavior Checklist**				.249
	Neurological comorbidity[a]	10.772	2.343, 19.202	.299*	
	Father's HRQOL[b]	-133.502	-27.363, -239.641	-.297*	
	Follow-up time	-1.090	-2.209, 0.029	-.227†	
	Youth Self-Report				.103
	Child not living with both parents[a]	15.853	0.502, 31.205	.365*	
	Teacher's Report Form				.416
	Father's HRQOL[b]	-0.304	-178.142, -27.790	-.304**	
	Neurological comorbidity[a]	6.352	0.053, 12.650	.230*	
	Follow-up time	-0.880	-1.762, 0.001	-.251†	
	Disease duration	1.311	-0.020, 2.642	.264†	
Internalizing Problems	**Parent-reported Child Behavior Checklist**				.278
	Mother's HRQOL[b]	-29.076	-57.201, -0.950	-.268†	
	Father's HRQOL[b]	-41.157	-82.690, 0.375	-.259†	
	Child not living with both parents[a]	3.016	0.433, 6.465	.202†	
	Follow-up time	-0.381	-0.776, 0.014	-.224†	
	Youth Self-Report				.094
	Follow-up time	-0.595	-1.197, 0.006	-.352†	
	Teacher's Report Form				.370

	Disease duration	0.687	0.259, 1.115	.376**	
	Father's HRQOL[b]	-43.123	-72.009, -14.238	-.346**	
	Child not living with both parents[a]	3.060	0.345, 5.775	.282*	
Externalizing Problems	**Parent-reported Child Behavior Checklist**				.112
	Father's HRQOL[b]	-44.872	-81.721, -8.023	-.306*	
	Child not living with both parents[a]	3.525	0.060, 6.989	.256*	
	Teacher's Report Form				.250
	Disease duration	0.546	0.158, 0.935	.353**	
	Father's HRQOL[b]	-33.829	-60.358, -7.300	-.320*	

ASEBA, The Achenbach System of Empirically Based Assessment; HRQOL, health-related quality of life; Tx, transplantation.

Note. The model included disease duration, follow-up time, neurological comorbidity, psychiatric diagnosis, child not living with both biological parents, mother's psychopathology score, and father's HRQOL. The model excluded all variables for Youth-Self Report Externalizing Problems as non-significant. The analyses included 57 patients for parent-reports, 30 patients for self-reports, and 51 for teacher-reports. A higher score in the ASEBA questionnaires indicates more problems. **p < .01, *p < .05, †p < .10

[a]Children not living with both biological parents, neurological comorbidity, and psychiatric diagnosis were coded as dichotomous variables. In all cases, 0 represents patients living with both biological parents and patients without neurological or psychiatric comorbidity. In contrast, 1 represents the presence of these risk factors.

[b]A lower HRQOL score indicates more problems.

5 DISCUSSION

The aim of this thesis was to report the cognitive and behavioral outcome of a national sample of pediatric organ Tx recipients in Finland, without excluding patients with neurological comorbidity. In cognitive outcome, a generalized effect on intelligence was observed on a group level in children with heart or kidney Tx, particularly in children with neurological or neuroradiological abnormality. Liver Tx children exhibited age-appropriate intelligence. In neuropsychological functions, all Tx groups exhibited specific visuomotor and visuoconstructive impairment. Neurological comorbidity, early onset of disease, longer disease duration before Tx, and – for kidney Tx children – poorer graft function at follow-up were important risk factors for cognitive outcome.

In behavioral outcome, no significant differences were observed in HRQOL or PSA between heart, kidney, or liver Tx children. More Internalizing and Total Problems emerged in parent and teacher-ratings, but not in self-reports. In self-reported HRQOL, however, lower ratings were observed in specific health dimensions. Longer follow-up time since Tx was associated with better behavioral outcome, and adolescents showed better HRQOL than did preadolescents. Neurological comorbidity was associated with both self-reported HRQOL and proxy-reported PSA, yet family structure and parental HRQOL also influenced the child's PSA.

5.1 Cognitive outcome

5.1.1 Intelligence

Reports indicate that children who have undergone organ Tx exhibit intelligence in the average to low-average range (LaRosa et al., 2011). The present study observed a generalized effect on intelligence of the suggested size after heart and kidney Tx with average group scores in the low-average or borderline range, while liver Tx children performed in the average range (see Table 4).

Lower FSIQ, compared to test norms or a matched control group, is a common finding in studies assessing heart Tx children (Baum et al., 2004; Ikle et al., 2003; Mahle et al., 2006; Wray et al., 1994; Wray & Radley-Smith, 2005) as well as in children with non-transplant cardiac surgery (Hülser, Dubowy, Knobl, Meyer, & Schölmerich, 2007; Karsdorp, Everaerd, Kindt, & Mulder, 2007; Miatton, De Wolf, François, Thiery, & Vingerhoets, 2007; Sarajuuri et al., 2007). Other studies of pediatric heart Tx have reported FSIQs of 80-89 on the Wechsler Intelligence scales (Baum et al., 2004; Ikle et al., 2003; Krishnamurthy et al., 2011; Mahle et al., 2006), which are well in line with our results (average FSIQ of 86). Cognitive impairment has been observed in infant heart Tx recipients, with 34% exhibiting mental delay, 41% language delay, 52% motor delay, and 48% delay in adaptive behavior defined as more than 2 SD below test norms (Joffe et al., 2011). In school-aged children, studies have reported below-average FSIQ in nearly one third of patients who underwent a heart Tx during their first year of life (Baum et al., 2004) and in almost half of the heart or lung Tx children transplanted at various ages (Brosig et al., 2006). In contrast, however, 26% of the heart Tx children in our study had below-average FSIQs. These results seem promising for school-aged children with heart Tx, especially in light of the more stringent exclusion criteria used in many previous studies. However, studies reporting the outcome of infant heart Tx recipients generally seem to suggest poorer cognitive outcome (Baum et al., 2004; Mahle et al., 2006), likely due to the more severe course of the disease (Karsdorp et al., 2007). Similarly in our study, congenital disease, number of heart surgeries, and pathological brain findings pre-Tx explained some of the deterioration in cognitive outcome, indicating an effect of disease severity.

For kidney Tx recipients, the average FSIQ of 84 reported in our study was poorer than that in earlier studies (values range between 87 and 103; Falger et al., 2008; Fennell et al., 1984; Lawry et al., 1994; Mendley & Zelko, 1999; Qvist et al., 2002). This may have resulted from younger age at Tx in our study as well as the different inclusion criteria. Many earlier studies have excluded patients with, for example, cognitive delay (Fennell et al., 1990; Mendley & Zelko, 1999). As a result, a comparably high percentage of our patients fell in the cognitively delayed range (i.e., below average, 18%). When children with neurological comorbidity (including

those with a diagnosis of mental retardation) were excluded from the analyses of the current study, the average FSIQ of the Tx group fell in the normal-average range (an average FSIQ of 91). However, performance was still statistically significantly below test norms. Similarly, Qvist and colleagues (2002) at the Childrens's Hospital in Helsinki found average intelligence in the patient group attending normal class (VIQ 92, PIQ 93), although when all kidney Tx children were included, both values were the lowest reported to date in the pediatric kidney Tx literature (VIQ and PIQ 88). This study also included children transplanted at an early age (Qvist et al., 2002). Another study that included all patients (Falger et al., 2008) used median values instead of mean values. When reported as median values, our kidney Tx sample had a mean FSIQ of 89, which is notably lower than that reported by Falger and colleagues (median FSIQ 97). Differences in study samples may have affected the results. Despite spending similar time on dialysis, our patients received transplants at a younger age and had poorer growth, which may indicate a more severe course of disease.

Liver Tx patients reached a relatively good general cognitive level, as evidenced by their mean FSIQ of 94, compared to that in previous studies of school-aged children assessed with the Wechsler Intelligence scales (FSIQ of 86-95; Adebäck et al., 2003; Kennard et al., 1999; Krull et al., 2003; Sorensen et al., 2011). In the pediatric liver Tx literature in particular, studies have employed a variety of exclusion criteria. Even though we included all patients, only 11% of our liver Tx patients had below-average FSIQs, compared to 4% to 27% in other studies (Adebäck et al., 2003; Gilmour et al., 2009; Kennard et al., 1999; Sorensen et al., 2011). Furthermore, studies report that 26% to 50% of liver Tx patients (compared to 11% in our sample) score in the borderline range, indicating a possible need for special education services (Adebäck et al., 2003; Sorensen et al., 2011). Additionally, all of our patients received an organ from a deceased donor, whereas many other studies report results from recipients of organs from both a deceased donor and a living relative. The latter has been associated with shorter disease duration, younger age at Tx, and possibly better cognitive outcome (Kaller et al., 2005; Kaller, Langguth et al., 2010; Schulz et al., 2003). On measures of global

intelligence, only PIQ differed significantly from the population mean. Thus, the cognitive outcome for the majority of our liver Tx patients is reassuring.

Approximately one third of our Tx patients had a significantly lower PIQ compared to VIQ. Previous studies have reported a significantly lower PIQ compared to VIQ in kidney and liver Tx recipients (Adebäck et al., 2003; Falger et al., 2008). However, not all studies have confirmed this discrepancy (Fennell et al., 1984). Overall, the results suggest that in a national sample of Finnish Tx patients, without excluding patients with neurological comorbidity, the majority had reassuring outcomes on measures of global intelligence. However, a significant minority exhibited a generalized effect on intelligence, mainly in association with neurological comorbidity. On the group level, heart and liver Tx children had similar, or slightly better, performance than that reported in previous research, yet kidney Tx children exhibited more global delay. The findings highlight the greater effect on PIQ, particularly on Block Design, compared to VIQ.

5.1.2 Neuropsychological profile

A pattern of effects was observed in the neuropsychological profiles of the Tx children. The greatest differences between the Tx groups and their matched control groups occurred on the paper-and-pencil tasks assessing visuomotor and visuoconstructive functions; scores for all Tx patients fell in the borderline range. On a non-motor visuospatial task, kidney and liver Tx children scored significantly lower than did their control groups, with a trend emerging in the heart Tx group. In addition, parental evaluations revealed an increased incidence of problems in motor skills and perception across groups. These visuomotor and visuoconstructive deficits were also observed in children without neurological comorbidity, who had a group mean of average intelligence.

Studies of infant heart (Fleisher et al., 2002; Freier et al., 2004; Joffe et al., 2011; Wray & Radley-Smith, 2005), kidney (Davis, Chang, & Nevins, 1990), or liver Tx recipients (Gilmour et al., 2009) often report delayed psychomotor development. Evidence is also mounting that visuomotor and visuospatial impairment is present in

school-aged children after heart (Baum, Freier, Freeman, & Chinnock, 2000; Baum et al., 2004; Mahle et al., 2006; Uzark et al., 2009), kidney (Falger et al., 2008), and liver Tx (Stewart et al., 1991; Yssaad-Fesselier et al., 2009). Immunosuppressive medication, which may cause mild tremor even at normal blood levels (Gijtenbeek, van den Bent, & Vecht, 1999), may account for part of this impairment. However, studies on children with surgically corrected heart diseases and children on the waiting list for either heart/heart-lung Tx or kidney Tx also show delayed psychomotor development in infancy or fine motor and visuospatial difficulties at school-age (Bellinger et al., 2003; Davis et al., 1990; Wray & Radley-Smith, 2004). Nevertheless, some improvement may occur post-Tx. An early study reported the greatest pre- to post-kidney Tx improvement in PIQ (assessed by Picture Completion, Block Design, and Object Assembly) and mathematics compared to a healthy control group (Fennell et al., 1984). More specifically, Mendley and Zelko (1999) found pre- to post-kidney Tx improvement on computer-based testing in motor-free decision speed, but not in motor speed per se (Mendley & Zelko, 1999). Taken together, these findings imply a possibly irreversible effect of childhood end-stage organ failure and consequent Tx on neuropsychological outcome, and that visuospatial, visuomotor, and fine motor functions are particularly sensitive.

Visuospatial impairments may underlie math difficulties reported by parents of Tx children in this study (Swanson, 2012). The current Tx children showed a more than two-fold increase in the incidence of full-time special education and two- to three-fold increase in part-time special education services over that of the general population due to their learning disability in mathematics (Official Statistics of Finland., 2009). The numbers of children in special education and children with low IQ scores were similar, except for the kidney Tx group. The amount of special education was less than expected from the number of kidney Tx children with IQs in the borderline or below-average range. In addition, only one heart Tx patient and three kidney Tx patients had been diagnosed with mental retardation (data not presented), although five heart, nine kidney, and two liver Tx patients scored below average (FSIQ < 70). This is in accordance with the results of other studies on children with solid organ Tx, where cognitive impairment and the need for interventions at school have been under-recognized (Gilmour et al., 2009; Kennard

et al., 1999). Some researchers have suggested that teachers may have different expectations for the school achievements of sick children (Wray et al., 1994). However, underachievement and poorer school functioning have also been associated with absence from school among heart and liver Tx children (Alonso et al., 2010; Wray et al., 2001). Thus, hospital schools play an important role in helping children maintain their school work during hospital stays.

In addition to shared difficulties in the neuropsychological domains of visuospatial, motor, and construction, other areas of neuropsychological functioning were also affected. Social perception has not earlier been assessed with standardized measures in this patient population. All Tx groups scored lower on a test of Affect Recognition than did their control groups. In children without neurological comorbidity, the significance remained only in the kidney and liver Tx groups. This test requires primarily the ability to read emotional expressions, but may also manifest as a secondary deficit following problems in visual discrimination, face recognition, working memory, or language (Korkman, Kirk, & Kemp, 2007b). The specific task of analyzing children's facial expressions may thus be difficult because of an impairment in visual perception. A related function, Memory for Faces, was intact, however. Previous studies have reported average face recognition in liver Tx children (Krull et al., 2003). The simpler task of face discrimination and recognition appears to be age-appropriate, yet the more complex task of reading and interpreting facial expressions is impaired. Results of questionnaire studies on social functioning have been mixed. Social functioning has fallen within normal limits when rated by both liver Tx patients and their parents (Gilmour et al., 2009; Schulz et al., 2003), but sometimes problems have been reported in all Tx groups (Alonso et al., 2010; Qvist et al., 2004; Wray & Radley-Smith, 2007). In this study, parents reported problems in social functioning on two different questionnaires, indicating a possible effect of disease and treatment on social functions. Teachers, on the other hand, reported no social problems.

Language and memory difficulties in our study were attributable mainly to a generalized cognitive impairment in the heart and kidney Tx children with neurological comorbidity. Hearing loss may have affected their language development and should be controlled for in this patient population (Bucuvalas et

al., 2003). In children without neurological comorbidity, impairment in receptive language occurred only in kidney Tx children. Numerous previous studies on pediatric organ Tx have reported language delays (Fleisher et al., 2002; Krull et al., 2003), often occurring together with visuomotor and visuospatial impairment (Baum et al., 2004; Mahle et al., 2006). Yet, others have found impairment mainly in PIQ, visuospatial, and fine motor functions (Brouhard et al., 2000; Falger et al., 2008; Stewart et al., 1991; Yssaad-Fesselier et al., 2009). Thus, certain risk factors may affect language development rather than visuospatial functions. In older children, language skills may have already developed, and adverse events are more likely to affect new or developing skills. According to a recent study, executive functions, visuospatial performance, and verbal memory are indeed skills that mature later than social perception and language (Korkman, Lahti-Nuuttila, Laasonen, Kemp, & Holdnack, 2012).

Despite their relatively good performance on the current tests of memory and learning, parents reported a significant increase in memory problems across Tx groups, and an increase in learning problems in kidney and liver Tx groups. Few other studies have included measures of memory functions. Reports indicate that liver Tx children score lower in memory and learning than do children with cystic fibrosis, though mean scores still fall in the average range (Krull et al., 2003; Stewart et al., 1991). Similarly, a large study of liver Tx children reported impaired working memory on computer-based testing when compared to the test norms, with mean scores in the low-average range (Kaller, Langguth et al., 2010). In kidney Tx children, performance on a working memory test requiring arithmetic skills improved from pre- to post-kidney Tx (Mendley & Zelko, 1999). Group-level memory and learning in the average range has been reported post-Tx, yet 20% performed at or below the borderline level (Qvist et al., 2002). Similarly, other studies have reported impairment in short-term memory after heart Tx (Wray et al., 1994). A test of Word List Interference confirmed lower working- and short-term memory in the heart and kidney Tx children in our study, yet the significance did not remain in children without neurological comorbidity.

In the Executive Functions domain, only Auditory Attention was assessed; of all the subtests in this domain, it has been shown to be the most sensitive to attention

deficit/hyperactivity disorder (Korkman, Kirk, & Kemp, 2007b). No difficulties were observed in the simple Auditory Attention task. The more complex task of the Auditory Attention and Response Set, where the child must shift and inhibit responses, was poorer in kidney Tx children than in their control group. Similarly, a significant increase in parent-reported problems in Executive Functions (including attention) in the Five to Fifteen occurred only in the kidney Tx recipients. Again, these attention problems were attributable mainly to the generalized effect observed in kidney Tx recipients with neurological comorbidity. Similarly, when assessing Tx children as one group, the ASEBA questionnaires revealed no self-, parent-, or teacher-reported attention problems. Questionnaire studies have reported conflicting results not only between studies, but also between raters, with teachers of liver Tx children reporting more executive problems and attention deficits than the children's parents reported (Sorensen et al., 2011). Standardized measures of attention have rarely been used in this patient population, though studies have attributed reduced attention to kidney failure (Gerson et al., 2006; Gipson, Duquette, Icard, & Hooper, 2007), and identified an improvement in sustained visual attention and stimulus discrimination sensitivity on a computerized continuous performance test from pre- to post-Tx (Mendley & Zelko, 1999). One study of kidney Tx children used a similar auditory attention task as the simple auditory attention task used in our study, and found no impairment (Fennell et al., 1984). Similarly, a previous study of kidney Tx children from the Childrens's Hospital in Helsinki found no group-level impairment in attention assessed by the NEPSY; however, 24% of kidney Tx children performed at borderline level or below average (Qvist et al., 2002). A recent study of liver Tx children found low average scores on a complex computerized attention test, with sustained attention particularly affected (Kaller, Langguth et al., 2010). Consequently, a computerized attention test, or a more complex task that includes both shifting and inhibition, may be more sensitive in detecting even subtle changes. Based on the visuospatial impairments observed, more problems may emerge in a visual (vs. auditory) attention measure. Clinical assessment of Tx children should also take into account the impact of emotional adjustment difficulties on attention and memory functions.

Although differences were observed between subtest scores, the overall shapes of the test profiles of heart and liver Tx children did not differ significantly from their control groups. More research assessing several neuropsychological domains in the same patients as well as associated risk factors are needed to further interpret these findings. Overall, the neuropsychological test profile of Tx children is in line with the observed effect on PIQ. The findings highlight the impact on visuospatial, visuomotor, and visuoconstructive functions. In the future, assessment of tremor is important in order to analyze its effect on the visuomotor difficulties. Only children with neurological comorbidity exhibited impairments in attention, language, and memory due to a more generalized effect on neuropsychological outcome in this group, except for receptive language impairment in kidney Tx children without neurological comorbidity.

The neuropsychological profile of Tx children, particularly after liver Tx, resembles that of nonverbal learning disorder described extensively by Rourke since the 1980s (Rourke, 1995), and which is still employed today (Forrest, 2004); research on the exact definition is ongoing. An early study by Stewart and colleagues suggested similar right-hemisphere dysfunction in pediatric liver Tx recipients (Stewart, Campbell, McCallon, Waller, & Andrews, 1992). Areas that have often been impaired in nonverbal learning disorder include visuospatial processing, motor coordination, social perception (emotional and nonverbal cues), mathematics, and the solving of novel and complex tasks (Semrud-Clikeman, Walkowiak, Wilkinson, & Christopher, 2010; Semrud-Clikeman, Walkowiak, Wilkinson, & Minne, 2010). The visuospatial problems are generally observed as a significantly poorer PIQ compared to VIQ as well as difficulties in copying complex figures (Semrud-Clikeman, Walkowiak, Wilkinson, & Christopher, 2010). However, the most essential defining features are still under debate and symptoms overlap considerably with other diagnoses, such as Asperger's syndrome. Hence, nonverbal learning disorder is not yet accepted in the Diagnostic and Statistical Manual of Mental Disorders and is, therefore, not a formal diagnosis.

Hypotheses attribute the cause of the symptoms associated with the nonverbal learning disorder to dysfunction in or damage to the white matter in the right hemisphere of the brain, which leads to dysfunction in intermodal integration

(Rourke, 1995). Evidence from an EEG study supports this hypothesis with long-distance gamma-band hypoconnectivity in the right hemisphere of children with the disorder (Njiokiktjien, de Rijke, & Jonkman, 2001). Further, a magnetic resonance imaging study has recently revealed benign brain abnormalities in the occipital or parietal regions in 25% of affected children (Semrud-Clikeman & Fine, 2011). However, because white matter anomalies regularly appear in various other childhood disorders, a critical review of literature on nonverbal learning disorder calls for more specific information on the type of white matter deficit to explain the symptoms (Spreen, 2011).

5.1.3 Organ-specific diagnostic subgroups

Differences in cognitive outcome between organ-specific diagnostic groups were difficult to establish. This is in accordance with previous studies. The lack of significant associations has resulted from small sample sizes limiting statistical power. However, it is quite well established that, because of its more complicated disease course, a diagnosis of CHD is associated with a more probable developmental delay both pre- and post-Tx than is a diagnosis of cardiomyopathy (Joffe et al., 2011; Wray & Radley-Smith, 2004). In a meta-analysis of children with non-transplant CHD, cognitive deficits were associated with disease severity, impacting PIQ in particular (Karsdorp et al., 2007). A diagnosis of CHD is associated with risk factors such as frequent heart surgeries, poor cerebral perfusion, and neuroradiological abnormalities (Licht et al., 2004). Similarly, in our sample, children with CHD had undergone corrective heart surgery pre-Tx, while none of the children with cardiomyopathy had undergone corrective heart surgery. Consequently, patients with CHD had a significantly longer disease duration pre-Tx than did patients with cardiomyopathy, yet their length of time on the waiting list were similar. Children with CHD presented with brain abnormality more often than did children with cardiomyopathy. Compared to children with CHD, children with cardiomyopathy may experience normal, or near normal, development with acute disease onset (Mohammad & Alonso, 2010).

Concern has grown about an adverse neurodevelopmental outcome in children with an initial diagnosis of CNF (Qvist et al., 2002; Valanne et al., 2004). These patients, with a lower gestational age and birth weight, are severely ill from birth (Huttunen, 1976; Patrakka et al., 2000) and undergo Tx at a significantly younger age than do children with other diagnoses. Yet, their cognitive outcome was surprisingly good; they had similar outcome as did children with other diagnoses. Interestingly, a trend for better functions in the visuospatial domain was observed. When children with CNF were compared to children with other congenital kidney diseases, this difference became significant. CNF children experienced significantly shorter disease duration than did children with other diagnoses, a result associated with better cognitive outcome. We are unaware of other studies reporting the cognitive outcome of CNF children only. Qvist and colleagues reported a high percentage of border zone infarcts on magnetic resonance imaging among the first kidney Tx patients at the Childrens's Hospital in Helsinki, the majority of whom had CNF (Qvist et al., 2002; Valanne et al., 2004). Similar to our results on patients with CNF, these first patients had no PIQ-VIQ split. These patients received kidney Tx between 1987 and 1995, while anti-coagulation treatment was introduced in 1989 as a routine treatment for patients with CNF. The majority of patients with border zone infarcts received no anti-coagulation treatment and suffered seizures and hypertensive crises prior to Tx (Qvist et al., 2002). Their long-term behavioral and educational outcome, however, have been comparable to those of patients without border zone infarcts (Haavisto, Jalanko, Sintonen, Holmberg, & Qvist, 2011), yet their long-term cognitive outcome has not been studied. Hypertension, seizures, and pulmonary edema among patients on peritoneal dialysis have since decreased (Holtta, Rönnholm, Jalanko, & Holmberg, 2000). Improved treatment and early Tx in this large diagnostic group seems to result in improved cognitive outcome.

In liver Tx patients, no differences emerged between those with biliary atresia, a congenital disease, and other diagnoses (both congenital and acquired). The first studies of pediatric liver Tx associated poorer cognitive outcome with early onset of liver disease and a diagnosis of biliary atresia (Stewart et al., 1989; Stewart et al., 1992). Studies of more recent patient cohorts have reported contradictory results regarding the influence of age at disease onset or at Tx (Kaller et al., 2005; Kaller et

al., 2010; Kennard et al., 1999; Schulz et al., 2003; Wayman et al., 1997). In a recent study, patients with biliary atresia had a better cognitive outcome than did those with other infantile onset liver diseases requiring liver Tx (Gilmour et al., 2009).

Overall, different diagnostic subtypes exhibit different disease courses and pathophysiology, which may affect cognition differently (Stewart et al., 1994). In heart Tx, children with CHD are generally at greater risk for cognitive impairments than are children with cardiomyopathy. In kidney Tx, children with CNF had similar outcomes as children with other diagnoses, except for less visuospatial impairment. In liver Tx, no effect of diagnosis (biliary atresia vs. other) emerged.

5.1.4 Risk factors for cognitive outcome

In heart and kidney Tx children, the greatest neuropsychological impairments – acquired mainly pre-Tx – occurred in patients with neurological or neuroradiological abnormality. These high-risk groups scored at or nearly 2 SD below average on the FSIQ, indicating significant cognitive delay, and had generalized difficulties across their neuropsychological test profile.

Congenital (vs. acquired) disease in heart and liver Tx patients, and longer disease duration in liver Tx patients were associated with lower visuospatial functions. Congenital disease was also associated with longer disease duration before heart and liver Tx. The opposite was true for kidney Tx, because children with CNF received Tx earlier in life than those with other congenital diseases. Thus, early, prolonged insufficiency of blood oxygenation in heart disease and the circulation of toxic substances before kidney and liver Tx seemed to lead to lower visuospatial processing, regardless of time on dialysis or bilirubin levels. The smaller effect on visuospatial processing in CNF supports these findings, since CNF in newborns specifically leads to loss of protein in urine and abnormally low levels of protein in the blood, with uremia being less common prior to nephrectomy (Jalanko, 2009). In heart Tx children, corrective heart surgeries, undertaken in patients with CHD were associated with lower Executive Functions, assessed by the subtest of Auditory Attention and Response Set. Similarly, a Finnish sample of children with univentricular hearts who had undergone one or more non-transplant

corrective heart surgeries scored in the borderline range in the Auditory Attention subtest of the NEPSY (Sarajuuri et al., 2007).

Longer follow-up time was in heart and kidney Tx patients associated with poorer scores in certain subtests. In the liver Tx group, however, longer follow-up time was associated with better scores. Follow-up times did not differ between groups. However, liver Tx children had a significantly shorter disease duration and waiting time for Tx than did children with a heart or kidney Tx. Longer disease duration could lead to poorer long-term rehabilitation even after Tx. However, liver Tx children also had better cognitive outcome in general. With their better cognitive capacity they may have been able to acquire new skills more efficiently in the post-Tx period compared to heart and kidney Tx children. A decrease in hand-eye coordination and arithmetic in short-term follow-up of heart Tx children have been reported previously (Freier et al., 2004; Wray & Radley-Smith, 2005; Wray & Radley-Smith, 2006). More studies on the longitudinal effect of heart disease and consequent Tx on visuospatial skills are needed. In kidney Tx children, weakened graft function may further have played a role in their long-term outcome. However, more research is needed in order to resolve this issue.

In kidney Tx patients, poorer graft function at the time of assessment associated with poorer language and memory skills as well as auditory attention. Kidney function has been associated with intellectual and academic outcomes in children with chronic kidney disease (Duquette, Hooper, Wetherington, Icard, & Gipson, 2007), and with memory functions in kidney Tx children (Fennell et al., 1990). In other studies, kidney function failed to correlate with cognitive outcome (Davis et al., 1990; Falger et al., 2008). Our patients had a poorer glomerular filtration rate than did patients in several previous studies (Mendley & Zelko, 1999). However, we used a measured glomerular filtration rate (^{51}Cr-ethylenediamine tetraacetic acid clearance), which yields stricter values than does an estimated glomerular filtration rate calculated, for example, with the Schwartz formula (Schwartz, Haycock, Edelmann Jr., & Spitzer, 1976). In addition, kidney function tends to deteriorate over time (Ortiz et al., 2005; Qvist et al., 1998; Qvist et al., 1999). While other studies have assessed patients approximately one (Davis et al., 1990; Fennell et al., 1984; Mendley & Zelko, 1999) or six years post-kidney Tx (Falger et al., 2008;

Qvist et al., 2002), our patients were assessed on average seven years (range 1-14 years) post-kidney Tx. In all heart and liver Tx children, graft function was normal at the time of assessment and, thus, its association to outcome was not analyzed. In the liver Tx group, the highest bilirubin level before Tx showed no association with later cognitive outcome. Earlier, Wayman and colleagues reported no association between parameters of disease severity (i.e., bilirubin and ammonia) and developmental outcome; parameters of malnutrition (i.e., albumin levels and poor growth before Tx), however, did show such an association (Wayman et al., 1997). In a more recent study, ammonia levels, associated with hepatic encephalopathy, and poor growth prior to liver Tx were specifically associated with lower PIQ and visuomotor integration (Gilmour et al., 2009). In our study, liver Tx children had the shortest disease duration, but showed the strongest correlations between disease duration and cognitive outcome, namely PIQ. Adding risk factors targeting malnutrition or using a cumulative value for pre-Tx blood values could have proved a more sensitive measure than a single measurement, even when using the highest value.

Bypass time during heart Tx surgery showed no association with neuropsychological outcome in our study. Studies have shown that, in children who underwent heart surgery, cardiopulmonary bypass and circulatory arrest carry neurodevelopmental risks, specifically in visuospatial and visuomotor skills (Bellinger et al., 1999; Bellinger et al., 2003). However, other studies of heart Tx children have found no association between cognitive outcome and bypass time during Tx (Wray & Radley-Smith, 2006). Lastly, outcome showed no association with parental education, gender, or prematurity.

Overall, numerous risk factors appear to affect developmental outcome. The greatest effect on cognitive outcome occurred in children with neurological comorbidity. Early onset and longer disease duration prior to Tx were associated with poorer cognitive functions, particularly visuospatial processing. In kidney Tx children, also graft function affected language skills, auditory processing, and memory.

Although no comparison between Tx groups was undertaken, liver Tx patients consistently performed the best across cognitive outcome variables, and kidney Tx

patients, the poorest. This cannot be explained by numbers of children with neurological comorbidity, which were the lowest among kidney Tx children. However, kidney Tx children had a severe disease course. They were the youngest at disease onset and Tx, had the longest waiting time for Tx, and had the shortest stature both at Tx and at assessment. They were also the only Tx group who had weakened graft function.

5.1.5 Mechanisms

The six heart Tx patients in this study who had undergone pre-Tx brain imaging had various findings. Earlier, more systematic studies have found a high incidence of periventricular leukomalacia both in newborns with CHD and in neonates undergoing heart surgery (Licht et al., 2004; Mahle et al., 2002). Besides younger age at surgery, identifiable risk factors for periventricular leukomalacia include a longer time on cardiopulmonary bypass, hypoxemia, and hypotension (Galli et al., 2004). Periventricular brain damage, associated with fine motor deficits in particular, but also with visuospatial difficulties in preterm infants (Jakobson, Frisk, Knight, Downie, & Whyte, 2001), may explain the deficits observed in the heart Tx population.

In end-stage kidney or liver disease, encephalopathy may develop. Some evidence in the adult liver Tx literature seems to indicate an adverse effect of pre-Tx hepatic encephalopathy on post-Tx brain volumes and neuropsychological functions (Garcia-Martinez et al., 2011; Sotil, Gottstein, Ayala, Randolph, & Blei, 2009). In addition, malnutrition prior to liver Tx and, in end-stage kidney disease, prior to the initiation of dialysis is of concern (Laakkonen, 2011; van Mourik et al., 2000), since malnutrition in early life can affect brain development (e.g., myelination) and later cognitive functioning (Majovski & Breiger, 2009; Wayman et al., 1997).

In all Tx groups, immunosuppressive medication causes hypertension (LaRosa et al., 2011). In kidney disease, however, hemodynamic changes already appear before Tx, particularly during dialysis. Hemodynamic crises have been associated with ischemic lesions in the zones between major arterial areas (i.e., the watershed areas),

as occurred in 54% of the first young patients treated with kidney Tx at the Childrens's Hospital in Helsinki (Valanne et al., 2004). Mild ischemic changes in the watershed areas have also been reported in children with univentricular hearts without Tx (Sarajuuri et al., 2007). Post-Tx, similar lesions in the watershed areas are evident in posterior reversible encephalopathy syndrome. Since this syndrome was first described in 1996 (Hinchey et al., 1996), and because our study involved patients transplanted between 1993 and 2007, this fairly recent diagnosis may have been overlooked. It presents as altered consciousness, seizures, headache, and/or visual abnormalities, with acute hypertension and immunosuppressive medication as common triggers (Erol et al., 2007; Onder et al., 2007). Disturbed cerebral autoregulation causes vasogenic edema in the watershed area. The prevalence of posterior reversible encephalopathy syndrome in the pediatric Tx population may be higher than in adults, in whom prevalence has been 0.6% among liver Tx recipients (Bartynski, Tan, Boardman, Shapiro, & Marsh, 2008). Incidence rates have been 10% in children with liver Tx (Erol et al., 2007) and 9% in children with kidney Tx or end-stage renal disease (Onder et al., 2007). Similar neurotoxicity has been reported in the use of OKT3 antibody in treating corticosteroid-resistant graft rejection (Parizel et al., 1997). In posterior reversible encephalopathy syndrome, the bilateral white matter signal abnormalities, seen mainly in the posterior cortical region, typically resolve within two weeks. However, subtle visuoperceptual abnormalities have been reported in short-term follow-up, after the cortical blindness resolves (Frutiger, Fennell, & Parsons, 1999). Its long-term neuropsychological effects are unknown.

Also, numerous other factors may have played a role. Growth hormone resistance has been reported in children with chronic liver disease (Maes, Sokal, & Otte, 1997), with hormone levels turning to normal after Tx (Sarna, Sipilä, Vihervuori, Koistinen, & Holmberg, 1995). Growth hormone and growth hormone mediators are affected in several ways also in kidney failure (Mahan, Warady, & Consensus Committee, 2006). A recent study has shown an association between growth hormone deficiency and abnormalities in white matter fiber density, as well as impaired global cognitive functioning and motor skills in children with isolated growth hormone deficiency (Webb et al., 2012). Growth hormone treatment has

been associated with improvement in visuospatial functions across different pediatric groups, although the mechanisms by which this occurs remain unknown (Cody et al., 2005; Hokken-Koelega, van Pareren, & Arends, 2005; Huisman et al., 2008).

To summarize, Tx children seem to be susceptible to negative effects in the posterior cortex and to exhibit associated visuospatial difficulties (Bear, Conners, & Paradiso, 2007). Hemodynamic changes have been reported in all Tx groups with diminished cerebral blood flow, hypoxemia, and hypotension in children with heart disease; hypertension and changes in blood pressure during dialysis; and post-Tx hypertension due to immunosuppressive medication. The watershed areas seem the most vulnerable to ischemic lesion resulting from altered cerebral blood flow (Bartynski et al., 2001).

5.2 Behavioral outcome

Although adult studies on long-term HRQOL have reported poorer outcome in kidney Tx recipients (Karam et al., 2003), our study supported the few studies conducted on pediatric patients that have reported similar HRQOL and post-traumatic stress symptoms regardless of Tx type (Devine et al., 2010; Mintzer et al., 2005). Similar to our study, previous comparison studies have had small sample sizes in at least one Tx group (Devine et al., 2010; Devine et al., 2011; Mintzer et al., 2005; Simons et al., 2008). Consequently, group sizes in pediatric studies may have been too small to detect statistically significant differences between Tx groups. Adjusting for disease duration and follow-up time in the present study may further have reduced power for detecting group differences by affecting variance. However, as this study presents one of the first comparison studies in the field, inclusion of covariates was considered the more conservative approach and was, therefore, chosen. Disease duration was used as a covariate because it varied significantly between the Tx groups and was associated with PSA. Follow-up time was used as a covariate because it correlated significantly with the outcome variable of HRQOL. However, results remained the same when disease duration and follow-up time were removed as covariates (data not presented). Other background variables analyzed in

Study IV that differed significantly between the groups (congenital disease, height at assessment, and immunosuppressive medication) correlated significantly with each other and the chosen covariates, and were, thus, not adjusted for. Their effect on outcome was evaluated in multiple regression analyses.

In our study, kidney Tx children still had stable graft function. However, HRQOL in kidney Tx children may change due to the unavoidable deterioration in kidney function, which may ultimately lead to dialysis and re-Tx (LaRosa et al., 2011; Limbers et al., 2011).

5.2.1 Health-related quality of life

In this study, a preference-based health utility measure was used for HRQOL. It is not directly comparable with the Child Health Questionnaire, for example, or the Pediatric Quality of Life Inventory (PedsQL®) used in most previous studies. Studies assessing health utility have used instruments developed mainly for the adult population, yet the valuation of health states between adolescents and adults seems to differ (Ratcliffe et al., 2012). A few studies reporting health utility after pediatric Tx have found decrements, but the specific domains in which problems arise vary (Apajasalo et al., 1997; Qvist et al., 2004; Tong et al., 2011). In our study, both preadolescent and adolescent patients experienced that their health made it more difficult to be with friends, and to attend school or to participate in hobbies. Besides missing school for regular hospital visits at the local hospital, all Tx children and adolescents had to travel to Helsinki for annual health check-ups, causing them to miss several days of school. Both age groups also reported excretion problems, which have been associated as a side-effect of immunosuppressive medication (Schonder et al., 2010). Eating and mobility problems occurred in patients with neurological comorbidity (i.e., cerebral palsy due to asphyxia, severe neurological complications, sensory neuropathy). Similar to adolescent patients in our study, long-term adult survivors of pediatric liver Tx have reported better vitality than healthy controls (Mohammad et al., 2012).

A discrepancy emerged in self-reports between preadolescent and adolescent patients. A similar discrepancy emerged in the first pediatric patients transplanted at the Childrens's Hospital in Helsinki and assessed with the same health utility measure. The authors hypothesized that this difference may have resulted from an altered perception of HRQOL after a life-threatening disease or denial due to fear of recurrence. However, in the first pediatric Tx sample, more preadolescent patients had more additional complications or diseases (Apajasalo et al., 1997). In our sample, the age groups did not differ with respect to neurological or psychiatric comorbidities. All patients received pre-Tx preparation and annual counseling as part of their treatment plan, and the medical treatment had changed little. However, preadolescents did have a shorter follow-up time, which was associated with lower HRQOL. Methodological issues may also have played a role, since the age groups completed different, albeit comparable, questionnaires. However, results remained also when comparing scores without their preference weight (data not presented), indicating more than a methodological bias. In younger children, studies have reported that parents did not provide their children with sufficient information (Gritti et al., 2001). It is therefore important to include patients, according to their developmental level, in their care, to describe procedures, and to discuss their thoughts about their state of health and its effect on their future. Health-care professionals are encouraged to help families maintain an open dialogue about their child's disease and Tx to avoid it becoming a "family secret".

5.2.2 Psychosocial adjustment

The increase in Internalizing Problems identified in parent reports was, as would be expected, attributable mainly to significant somatic complaints in 24% of the Tx patients. Items reflecting somatic complaints included nightmares, constipation, feelings of dizziness, excessive fatigue for no apparent reason, and physical problems with no known medical cause (e.g., aches or pains, nausea, and rashes). Similar side-effects have been reported in previous studies (Schonder et al., 2010; Taylor et al., 2009; Uutela et al., 2009). Although parental HRQOL did associate with parental evaluations of other PSA problems in their child, it did not associate

with evaluations of somatic complaints. The parents of Tx recipients have reported more problems in health and physical functions than have the patients themselves (Sundaram, Landgraf, Neighbors, Cohn, & Alonso, 2007), which is in accordance with our results. Adolescents may compare their health to their pre-Tx state, while parents may compare their child after Tx to the child's same-aged healthy peers (Sundaram et al., 2007; Tong et al., 2011). Similarly, parents have more often reported PSA problems than have the adolescents themselves (Devine et al., 2010; Wu et al., 2008). In this study, it was impossible to determine whether adolescents had adjusted to their post-Tx condition or whether their strive for normalcy, as reported in other studies (Taylor, Franck, Dhawan, & Gibson, 2010; Wise, 2002), may have caused them to overlook their symptoms. It is also impossible to determine whether parents had a more accurate perception of their child in relation to age-expectations or whether they over-reported problems due to parental overprotectiveness of a chronically sick child. However, because of the generalized increase in PSA problems, behavioral, emotional, and social problems should be screened routinely in pediatric Tx recipients. Moreover, when the child experiences challenging events (e.g., medical complications, natural developmental stages, or adverse family events), psychosocial support should be readily offered.

Teacher-reports have seldom been included. As did a previous study from the Childrens's Hospital in Helsinki, we found that parents reported more problems than did teachers (Qvist et al., 2004), indicating that Tx children may be doing psychosocially relatively well in the classroom. Our good long-term outcome may also reflect the ambition at the Childrens's Hospital in Helsinki to make a school visit when a Tx patient begins school, informing both classmates, teachers, and the school nurse about the Tx. Increasing awareness and openness is likely to improve adjustment to school and decrease the risk for bullying. Overall, proxies in our study reported more generalized PSA problems than did youth self-reports. Also, no association was found between teacher- and self-reports. Parents and teachers may be cautious about even small indications of emotional and behavioral problems in Tx children. Because of the discrepancies in reports, it is important in both research and clinical work to gather information from several sources. Some problems,

particularly neuropsychological ones, may be easier to identify in the school environment and others at home.

5.2.3 Risk factors for behavioral outcome

Of the disease-related variables, longer follow-up time was associated with better HRQOL and fewer somatic complaints, which may at least partially stem from a decrease in the side-effects of medication or in the effects of adverse medical events. While side-effects from medication decrease with time, the risk for developing a secondary chronic disease increases. Both factors have been found to negatively impact HRQOL (Simons et al., 2008; Taylor et al., 2009). However, these late effects may not have appeared in the follow-up times in this study. Longer follow-up time was also associated with less PSA problems, indicating better adjustment with time. This association was likely pronounced in our study, since follow-up times varied extensively from 1 to 15 years. Children with an acquired disease exhibited better HRQOL, but showed no difference in PSA. In earlier studies, acute disease and consequent Tx in adolescents associated with more post-traumatic stress symptoms than did chronic disease because of its sudden and life-changing course in previously healthy children (Mintzer et al., 2005).

Longer disease duration was associated only with teacher-reported PSA problems. Also, longer disease duration in our patient sample was associated with poorer neuropsychological outcome. Thus, longer disease duration may impact learning and coping at school, even though the effects may not be evident in the home environment. Since teacher-reports have seldom been included, it is difficult to compare these findings to others. Other disease-related variables (i.e., age at Tx or at assessment, height at assessment, or type of immunosuppression) showed no association with outcome.

Many family-related variables were associated with PSA. Lower parental HRQOL was associated with more parent-reported PSA problems in the child, while only the father's HRQOL was associated with teacher-reported PSA problems. Earlier, parental physical functioning has been associated with self-reported physical

functioning among Tx adolescents (Simons et al., 2008). Including a variable on parental psychopathology has been suggested (Wu et al., 2008); it may be a more accurate measure than parental HRQOL. More studies that include parental wellbeing and teacher-ratings are needed to analyze the relevance of these findings.

Another family-related variable that predicted PSA problems was a family structure where the child was not living with both biological parents, an association previously reported in a Finnish epidemiological study (Luoma et al., 1999). In our study, not living with both biological parents involved the alternatives of living with one parent or alternating between divorced parents, step-parenting, the death of one parent, foster care, and adoption. The number of Tx children living with both their biological parents was similar to that in the general population (73% vs. 75%; Statistics Finland, personal communication, 8 June 2012). Previous studies have found no association between marital status and behavioral outcome after Tx (Devine et al., 2010; Simons et al., 2008). Family structure may be a more sensitive measure. Previously, family conflict and impaired family functioning have been associated with poorer HRQOL in children and adolescents who have undergone organ Tx (Devine et al., 2011; Simons et al., 2008; Taylor et al., 2009). Even when family functioning was normal (Alonso et al., 2008), parents of pediatric Tx recipients commonly reported increased emotional stress, disruption of family activities (Alonso et al., 2008), and greater adjustments to family routines (Denny et al., 2012). These findings stress the importance of the holistic approach of treating young patients together with their families. The parents should regularly be asked about their own and the family's wellbeing and receive counseling, if needed. In contrast to our expectations, parental educational level showed no association with outcome. However, parental education was classified as only two levels, which may have led to low sensitivity.

Neurological comorbidity was an important risk factor for post-Tx PSA and HRQOL. Previous research has found an elevated risk for emotional and behavioral problems in chronically ill children, especially those with neurological disorders (Hysing, Elgen, Gillberg, & Lundervold, 2009). Similarly, more PSA problems emerged in kidney Tx recipients with neurological comorbidity (Qvist et al., 2004).

The classification of neurological comorbidity in the current study was broad, and the impact could vary greatly between patients.

Psychiatric history has been associated with poorer psychological functioning in liver Tx children (Taylor et al., 2009). The number of children who had received psychological or psychiatric support after Tx was 22%, a percentage very similar to that in our study (26%). In most of our patients, a psychiatric diagnosis equalled mild to severe depression or post-traumatic stress disorder often related to the somatic disease, which would be expected to raise the Internalizing Problems score. However, the only outcome associated with psychiatric diagnosis was self-reported HRQOL.

Overall, longer follow-up time and the absence of neurological comorbidity were important alleviating factors for behavioral outcome. The findings also highlight the impact of family structure and parental wellbeing; factors which have also been associated with PSA in healthy Finnish children (Almqvist et al., 1999; Sourander et al., 2006). Many of these risk factors have been associated with nonadherence to immunosuppressive medication, which is a recognized problem in adolescents with possible graft loss and death as outcome. The transition from pediatric to adult care is a particularly vulnerable period (Fredericks, Lopez, Magee, Shieck, & Opipari-Arrigan, 2007; LaRosa et al., 2011).

5.3 Limitations of the study and suggestions for further studies

This thesis presents a single-center study, and the results may differ between centers depending on, for example, health care (including psychosocial support, neuropsychological assessment, and rehabilitation services), Tx listing criteria, survival rates, and sample demographic characteristics. Small group sizes, differing diagnoses, and large intragroup age ranges may have made it more difficult to demonstrate statistically significant differences between groups.

Studies I-III included all patients, even patients with re-Tx and combined liver-kidney or heart-lung Tx. We approached these challenges by using neuropsychological tests designed for a wide age-range. All children could be

assessed with the same measures, yielding results that were generalizable across ages. Information also came from parents, thereby ensuring data from multiple sources. Further, the studies also included a healthy control group.

WISC-III was published in 1999 and, consequently, has older norms than the NEPSY-II, published in 2008. It is also more reliable to compare results to a matched control group than to test norms. Thus, the results on the WISC-III may be taken as an orienting evaluation and the NEPSY-II results as the main results. On the Wechsler Intelligence scales, gains in scores generally emerge over time, particularly on the performance scale (Wechsler, 2003). Thus, the difficulties observed in the WISC-III in the Tx children might be even more pronounced when compared to the new normative data of the WISC-IV.

Study IV was one of the first exploratory studies to compare behavioral outcome in three pediatric organ Tx groups. Future studies should replicate the findings with larger group sizes. Similarly, the number of children eligible to complete the youth self-report of PSA was limited and no Finnish norms for the ASEBA questionnaires were available. This posed no problem when comparing raw scores between Tx groups. However, the rates of children with clinically significant problems should not be taken as prevalence rates, since the rates reflect U.S. norms. The number and type of assessed risk factors were limited, and numerous other risk factors may have affected PSA and HRQOL (e.g., medication side-effects, secondary chronic disease, rejection episodes). Systematic collection of these data may prove helpful in assessing their importance (Taylor et al., 2009). Only ten kidney patients received a living-related donation, so its impact could not be analyzed.

The generalizability of this study is quite good - the majority of eligible patients were recruited without exclusions. In the future, more multicenter studies and studies using a multi-informant approach are needed. No study thus far has compared neuropsychological outcome between heart, kidney, and liver Tx children. The latter has been proposed for determining similarities and differences in neuropsychological profiles (Fine et al., 2004). Assessment of adaptive behavior should be included in addition to cognitive tests to further analyze everyday functioning particularly in children with IQ scores below average. Measures of adaptive functions have, however, not yet been standardized in Finland. More

knowledge is also needed on brain mechanisms underlying cognitive effects. In behavioral outcome, qualitative interviews and studies on parent-child attachment would shed light on the emotional development of Tx children. Also, intervention studies for behavioral outcome are needed.

6 CONCLUSIONS AND CLINICAL IMPLICATIONS

The first conclusion of this study is that a generalized effect on global intelligence can be observed in children who have undergone a heart or kidney Tx, particularly in children with neurological or neuroradiological abnormalities. Nevertheless, the presence of mental retardation and, in kidney Tx children, the need for special education services tend to be under-recognized.

Second, in neuropsychological functions, a notable minority of patients had difficulties in visuomotor and visuoconstructive functions as well as in social perception, suggesting the need for further attention to nonverbal learning disorder in this patient group. Our results suggest that few problems emerge in attention, memory, and language. Evidently, assessment of global intelligence is insufficient, but needs to be complemented with a comprehensive neuropsychological evaluation. This patient group will require more special education services and remedial resources than unaffected children require, with special attention to their visuospatial processing and possible secondary problems in mathematics. They may also need support for their social perception and social skills. Since work requiring heavy physical effort may not be an option for all Tx children, optimizing learning is of great importance, as it improves future schooling and job opportunities. Of the risk factors, early Tx with shorter disease duration alleviated later cognitive outcome, particularly visuospatial functions, while neurological comorbidity strongly associated with global cognitive impairment. Further, poorer graft function at the time of assessment associated with lower verbal/auditory functions and memory in kidney Tx children.

Third, organ type does not appear to have a major impact on HRQOL or PSA after pediatric Tx. Rather, Tx recipients share common threats to their well-being. Improved treatment in order to avoid comorbidity (e.g., neurological sequelae), will improve outcome, but may be counteracted in the future by extended inclusion criteria for Tx. Longer follow-up time after Tx was associated with improved HRQOL and PSA, but family-related variables are also important for the child's adjustment. Consequently, families should routinely receive psychosocial support to

alleviate parental stress and family dysfunction for the benefit of the child. For the Tx child, new issues may arise during different developmental stages, and counseling as a routine part of treatment throughout childhood and adolesence is essential.

Appendix 1. Additional clinical data for the 87 transplant patients who participated in the study

	Mean ± SD	Range
Heart (*n* = 19)		
By pass time during heart Tx, min	175.2 ± 70.3	93.0-341.0
Previous corrective heart surgeries (yes/no), *n* (%)	7 (37%)	2.0-6.0
Left ventricular ejection fraction, %[a]	65.5 ± 6.1	54.0-77.0
Fractional shortening, %[b]	35.4 ± 5.3	28.0-46.0
Normal echocardiogram, *n* (%)	19 (100%)	
Kidney (*n* = 50)		
Time on dialysis pre-Tx, years	1.4 ± 1.2	0.01-5.8
Glomerular filtration rate, ml/min/1.73 m^2 [c]	47.5 ± 14.8	14.0-88.0
Serum creatinine, μmol/L[d]	98.7 ± 62.3	38.0-452.0
Liver (*n* = 18)		
Highest bilirubin level pre-Tx, μmol/L[e]	524.9 ± 409.7	11.0-1279.0
Galactose elimination capacity, min[f]	10.5 ± 1.3	8.0-13.0

Tx, transplantation.

Note. Data presented as mean ± 1 standard deviation and range, unless otherwise specified. Four children with a combined liver-kidney Tx are included in both the kidney and liver groups. Organ function was evaluated at the time of assessment.

[a]Normal value: 55-75%.

[b]Normal value: 28-38%.

[c]Glomerular filtration rate was measured by ^{51}Cr-ethylenediamine tetraacetic acid clearance (ml/min/1.73 m^2). Normal values > 90 mL/min per 1.73 m^2, near normal > 60 mL/min per 1.73 m^2.

[d]Normal values for children aged 6–12 years, 10–76 μmol/L; girls aged 13–16 years, 15–90 μmol/L; and boys aged 13–16 years, 20–95 μmol/L.

[e]The highest serum or plasma bilirubin level before Tx was selected as an indicator of disease severity. Since bilirubin as a disease severity marker is irrelevant in ornithine carbamoyltransferase (OCT)-deficiency and hyperoxaluria, bilirubin values for patients with these diagnoses were not recorded. This information was missing for one child who underwent Tx abroad. Normal values: 4–20 μmol/L.

[f]Galactose elimination capacity was expressed as the half-life of its clearance (min). Normal elimination time < 15 min.

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